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The Journal of Pediatrics

VOL. 9 SEPTEMBER, 1936 No. 3

Original Communications

MEDITERRANEAN DISEASE—THALASSEMIA (ERYTHROBLASTIC ANEMIA OF COOLEY)

ASSOCIATED PIGMENT ABNORMALITIES SIMULATING HEMOCHROMATOSIS

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ROCHESTER, N. Y.

THIS interesting disease presents three important abnormalities together characterizing a syndrome which may be designated "Mediterranean disease." The anemia alone is not a diagnostic factor and is usually associated with a progressive splenomegaly. The bone changes alone are not diagnostic, as very similar changes have been reported in sickle-cell anemia[21, 9] and hemolytic jaundice.[19, 6] The pigment abnormalities are of fundamental importance but alone do not make the diagnosis as we may find exactly similar pigment deposits in adult cases of hemochromatosis.

The disease is also limited to the people who live about the Mediterranean—Italians, Greeks, Syrians, Armenians—and shows a strong familial tendency. We have reported the disease in identical male twins, and, if one would explain such coincidences on the probabilities of chance, it is necessary to indulge in astronomical figures. Obviously there is some *inherited defect* which is responsible for the total abnormality involving hemopoietic tissues, bone growth, and pigment metabolism.

We reported in detail four years ago the clinical and autopsy findings in a typical case of this disease.[22] As the *pigment abnormalities* there described had not been noted in other published reports, we could not stress the importance of these findings. We now report in detail three more cases with complete autopsy reports. We have had opportunity to study certain organ tissues from two other cases kindly sent us by Dr. T. B. Cooley. All this material gives us reasonable security in our belief that the *pigment deposits are just as characteristic of this*

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Presented in abstract before the American Pediatric Society, June 11-13, 1936, Lake George, N. Y.

disease complex as are any other factors. The pigment abnormalities simulate hemochromatosis in the adult and are remarkably uniform. Iron-containing pigment is abundant in liver, pancreas, lymph glands, gastric mucosa, thyroid, and adrenals. The same pigment is usually demonstrable in Brunner's glands, salivary and mucous glands, parathyroids, hypophysis, heart muscle, kidney tubules, spleen, and bone marrow. Pigments normally present in the body—for example the reticular zone of the adrenal, the epidermis, the choroid plexus and the interstitial cells of the testis—are as a rule increased in amount in these cases.

This disease presents a uniform *clinical picture* consisting of a progressive anemia beginning usually during the first two years of life and terminating in death in most instances before adolescence. The blood picture, though not distinctive, is uniform and is characterized by marked irregularity in the size and shape of the red cell, fragmentation, and erythroblastosis. All stages of erythropoiesis may be seen in the peripheral blood. The hemoglobin distribution within the matured red cell may be very irregular. After splenectomy showers of nucleated red cells always occur.

Definite *retardation of growth* results. In Case 8 (E. S.) only two carpal centers of ossification were found at four years while her normal twin sister had four.

As the disease progresses, the typical mongoloid features develop, probably because of bone changes. In certain cases the icterus index of the blood is slightly elevated but lends little support to the idea formerly entertained, that the disease is due to hemolysis.

Enlargement of the spleen is proportionally greater than that of the liver, but, when the former is removed, the latter seems to increase in size.

To this group of clinical features the addition of the interesting abnormalities which occur in the bones, the unusual pigment disturbances, and the racial and familial distribution completes a characteristic syndrome.

LITERATURE

It is not necessary to review the literature of this disease as this has been done adequately in recent papers by Baty, Blackfan and Diamond,[1] Parsons and Hawksley,[13] and Yaguda.[23] Yaguda suggests that the erythroblastosis of the newborn be classified with this disease as described by Cooley, but we can see no merit to this suggestion and feel that it would only lead to confusion. Cooley did a great service when he defined clearly the clinical syndrome designated by him as "erythroblastic anemia" and separated it from a group of unrelated anemias and splenomegalies. The erythroblastoses of the newborn have only one thing in common with this disease *(thalassemia)*, but they are not racial, nor do they show bone and pigment abnormalities.

Anemia and erythroblastosis in these children is not sufficient alone to make the diagnosis, as Bennett, Hunter and Vaughan[2] have reported an identical blood picture in adult celiac disease or idiopathic steatorrhea. This anemia, however, yields to iron therapy.

It has also been pointed out by Baty, Blackfan and Diamond[1] that the marrow changes found in these children *(thalassemia)* are similar to the marrow histology of pernicious anemia during relapse. Their report gives admirable illustrations of marrow and spleen histology. We have been impressed with the *variety of changes* which may be found in the marrow and spleen in our material. Possibly the picture may vary

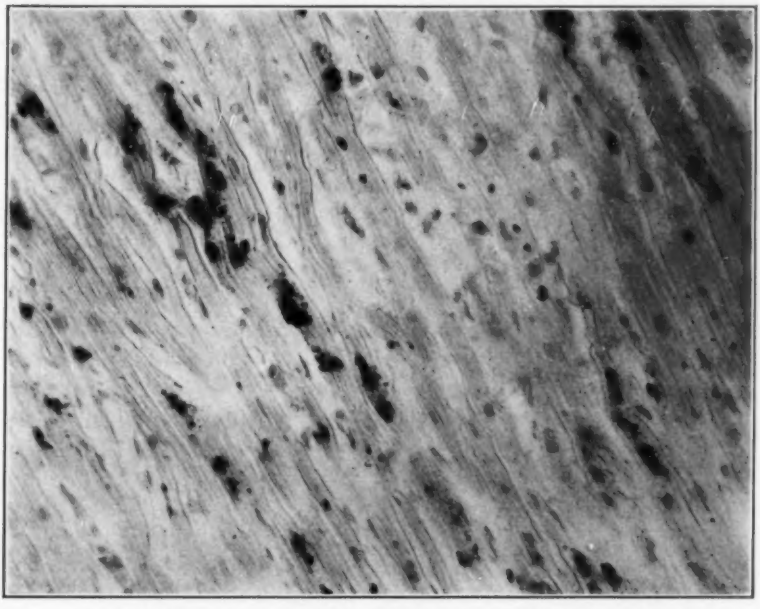

Fig. 1.—Case 4. Photomicrograph of heart muscle showing black grains of iron-containing pigment (magnification ×425).

somewhat depending upon the stage of the disease which happens to be represented. Both spleen and marrow may show chronic states of hyperplasia in which stroma and "foam cells"[22] may dominate the picture in contrast to the active cellular stages often illustrated.[1] These "foam cells" have been noted by others,[7] and at least in one case led to the diagnosis of Gaucher's disease from an examination of spleen alone.[12]

GENERAL PATHOLOGY OF THALASSEMIA

This is a composite picture of the autopsies studied by us. The mongoloid features are usually definite. General edema is quite common and may be related at least in part to the anemia. The fluid in

the serous cavities may be of a yellow color but usually shows no urobilin and no bile pigment. The anemia is probably also responsible for the fatty changes noted in the liver, heart, and kidney.

Heart may be enlarged, is pale and decidedly brown in color. Fine fat droplets and excess pigment are found in the heart muscle cells. Some of the pigment is lipochrome and some gives a strong test for iron (Fig. 1). This iron staining pigment is not always present.

Lungs usually show edema and perhaps bronchopneumonia.

Liver is enlarged and shows a deep buff or bronze color. The surface is smooth, and the lobulation is regular. The liver cells show fat droplets usually conspicuous in the center of the lobules. The liver cells are filled with a fine granular yellow pigment, most of which gives a strong test for iron. This pigment is more abundant in the marginal half of the lobule. *Chemical analyses* show about ten times the amount of iron found in normal liver tissue. The pigment is found almost wholly in the hepatic epithelium and not at all in the biliary duct epithelium. Kupffer cells show some pigment which is usually non-iron containing. Marrow cells in small nests may be found in some cases in the capillaries of the liver lobules. Gallbladder mucosa may show a brown color because of granular yellow pigment in the mucosa and the submucosa, and it is negative for iron.

Pancreas may be very distinctive grossly and presents a deep buff or bronze color. It is of normal size and is not indurated. The acinar cells may be very rich in granular yellow *pigment* much of which reacts to iron stains (refer to our first paper[22] for illustrations). This pigment is found only rarely in the epithelium of the islets but is commonly more abundant in the acini close to the islets. This distribution may be related to vascular supply.

Serous and Mucous Glands.—The mucous glands of the pharynx and trachea as well as the salivary glands usually show pigmentation, and much of this pigment reacts strongly with iron stains.

Gastrointestinal Tract.—The *stomach* in gross may show a deep pigmentation, often confused with postmortem staining. The acinar epithelium in this mucosa may be very rich in a yellow granular pigment which stains for iron. The chief cells and not the acid cells contain most of this pigment (refer to our first paper for illustrations[22]). Duodenum, jejunum, ileum, and colon show no iron-staining pigment in their mucosa, but *Brunner's glands* in the duodenum often do contain iron-staining pigment granules in the epithelium. The smooth muscle of the intestinal tract does not show deposits of pigment.

Genitourinary Tract.—Kidneys are a little enlarged and pale. There is usually a brownish color noted. Pigment is found in the epithelium of some tubules but not in others. Henle's tubules are often outlined by this pigment deposit (Fig. 2), some of which stains for iron and some not. Glomeruli, stroma, and collecting tubules are usually nor-

mal. Fat stains show a good many fat droplets in the convoluted tubular epithelium. A few casts are often present. *Bladder* is usually pale

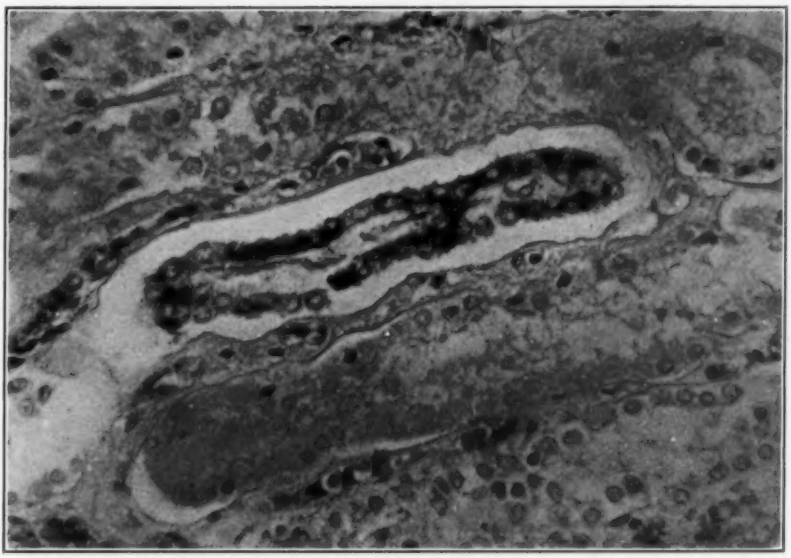

Fig. 2.—Case 4. Photomicrograph of kidney tubular epithelium containing black grains of iron-staining pigment (magnification ×425).

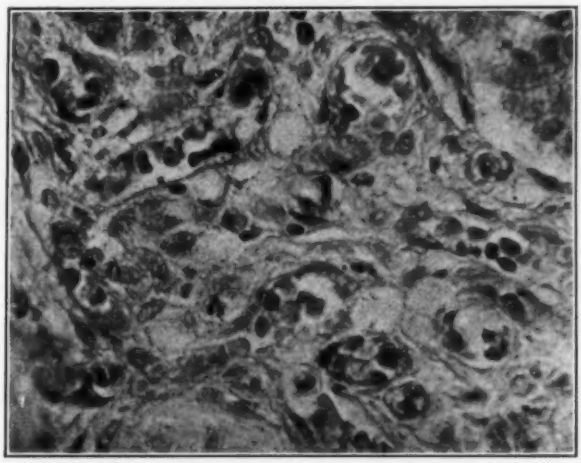

Fig. 3.—Case 5. Photomicrograph of testis with fine black grains of iron-containing pigment in the endothelium of several capillaries (magnification ×700).

and normal. The prostate is usually normal and nonpigmented but the immature acini in some cases may show lipochrome. *Testis* shows a

deep brown color in gross and much pigment in sections. Coarse granular pigment, which is negative for iron, is found in the interstitial tissue. Fine pigment grains rich in iron are often found in the capillary endothelium of the testis (Fig. 3) but the immature seminiferous tubules usually contain no pigment. Ovarian tissue shows nothing of interest.

Spleen is always much enlarged and may approximate one-half the size of the liver. It may show infarcts and adhesions. The gross picture suggests a chronic process; the organ is firm and hard and presents a sharp cut surface which is not velvety, suggesting much connective

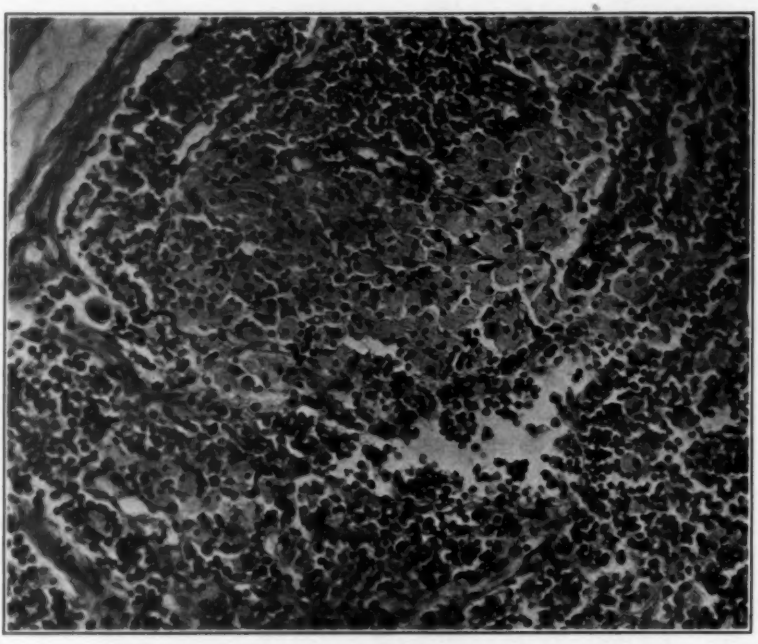

Fig. 4.—Case 3. Photomicrograph of retroperitoneal lymph gland which shows metaplasia: megakaryocyte (left), myelocytes (below), and foam cells (center), as well as normal lymphocytes (above), and gland capsule (left) (magnification ×300).

tissue increase. The histology varies with the stage of the disease, its rapidity of progress, and probably many other factors. The *lack of pigment* is conspicuous, and the spleen contains little iron in contrast to the liver and pancreas. *Chemical analyses* show less iron than normal (15 to 30 mg. per 100 gm. of fresh tissue). There is evidence of metaplasia and marrow activity in some areas of the spleen, with myelocytes, nucleated red cells, and megakaryocytes. Other parts may show accumulation of foam cells and great stroma increase. These foam cells at best give a faint pink color with fat stains. The malpighian corpuscles are

approximately normal but may be small. The trabeculae may show hyaline changes and in such areas often show deposits of iron and calcium.

Lymphatic Tissue.—The lymph glands are usually much enlarged and may have a definite pink color or again a definite brown color like the liver. This includes cervical, bronchial, retroperitoneal, and mesenteric glands. *Pigment* is a conspicuous feature and is abundant in the gland sinuses as though coming into the gland from tissues outside of the gland. Much of it stains strongly for iron, but the larger pigment granules often do not stain for iron. Some may give a positive stain for hemo-

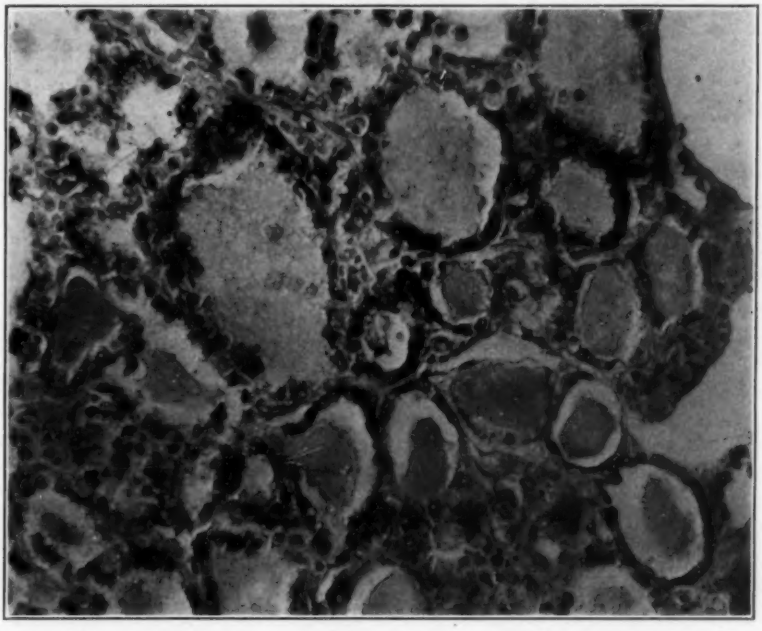

Fig. 5.—Case 5. Photomicrograph of thyroid. The alveolar epithelium is filled with black grains of iron-staining pigment (magnification ×365).

fuscin. Marrow metaplasia is seen in a few glands, and we may observe nests of myelocytes, nucleated red cells, and megakaryocytes. Foam cells are found in some lymph glands (Fig. 4). The germinal follicles are usually normal and appear active, but occasionally we observe a granule of iron-staining pigment in these cells. The solitary follicles and Peyer's patches of the intestine are usually normal. Only rarely is a cell noted containing a few granules of iron-staining pigment.

Thymus shows moderate regressive changes but no pigment deposits.

Blood Vessels.—Some of the moderate sized arterioles of the lungs, kidney, and mesentery may show accumulation of fine yellow granules

of iron-free pigment in the smooth muscle layers. *Endothelium* may contain iron-staining and iron-free pigment in the capillaries of the spleen, testis, thyroid, liver, lymph glands, and striated muscle.

Ductless Glands.—Thyroid is always strongly pigmented and in gross presents a deep brown color. The acinar epithelium is rich in fine yellow pigment granules which give a strong test for iron (Fig. 5). No pigment is found in the colloid. The general structure appears normal, and the epithelium is well preserved. *Parathyroids* are usually normal but in some cases present a small amount of fine pigment granules

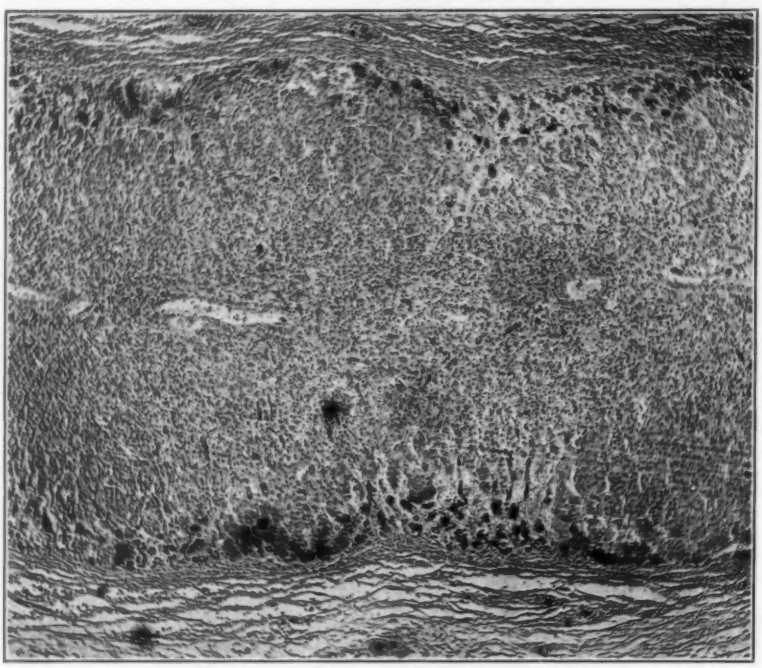

Fig. 6.—Case 5. Photomicrograph of adrenal cortex with iron-staining pigment as black granules in the glomerular zone only (magnification ×70).

which stain for iron in the cell protoplasm. *Adrenals* as a rule are smaller than normal and show a thin highly pigmented cortex. Iron-staining pigment is abundant in the glomerular zone (Fig. 6) and finely granular noniron-staining pigment is abundant in the reticular zone of the cortex. The medulla is normal.

Hypophysis may be somewhat pigmented and sometimes shows iron-staining pigment in the glandular portion. The general structure is normal. *Skin* is somewhat pigmented in gross, but in these races the skin is rather dark. There may be a little increase of yellow pigment in the basal cell layer of the skin, but we have never observed any iron-

staining pigment in this area. *Muscles* show no abnormal pigmentation except the heart (Fig. 1). The striated skeletal muscles are rather paler than normal and show no evidence of pigment except rarely in the endothelium of capillaries a granule of iron-staining pigment.

Bones and Marrow.—The changes in the *bone* are of two types: an *atrophy* of the bone trabeculae and shafts of various bones and a *proliferation* of new bone of rather delicate structure in association with the characteristic thickening of the calvarium, which shows peculiar radial markings in the x-ray film. The ribs as a rule show this same proliferation which causes a fusiform thickening in the rib shaft usually close to the tubercle and not extending much beyond the axillary line.

Marrow changes have been described frequently and pictured by us[22] and others.[1] There is a great marrow hyperplasia as in primary anemia, and the parent stem cells of the marrow are very abundant. Nucleated red cells are numerous. Myelocytes of all types are numerous. Megakaryocytes are numerous and normal. Phagocytes are present in goodly numbers and many contain hemosiderin in small amounts. The foam cells may occur in small or large islands, and there may be in places some fibrosis of the marrow.

CASE 3.—(No. 19247.) J. S., an Italian boy, was born Oct. 29, 1928, and died Oct. 31, 1933. The clinical record in detailed chronologic order from birth until Oct. 6, 1931, was published in our first report.[22] Since it has been possible to study this case in detail throughout life, the remainder of the clinical course is described in similar manner below.

The sixth admission (Oct. 6 to Oct. 31, 1931) was when the boy was three years old.

October 6: The blood count was as follows: red cells, 2,600,000; white cells, 33,600; hemoglobin, 30 per cent. The differential count was as follows: polymorphonuclears, 37.5; eosinophiles, 0.5; lymphocytes, 59; mononuclears, 3. A smear showed marked anisocytosis, poikilocytosis, some basic stipling, a few Howell-Jolly bodies, and many nucleated red cells (258 per hundred white cells).

Roentgenograms of the skull and upper extremities suggested that the bone changes had increased since the last examination on June 24, 1930.

October 7: The blood uric acid was 4.0 mg. per 100 c.c.; the plant pigments, 0.088 mg. per 100 c.c.

October 8: The following measurements were found; circumference of head, 52.5 cm.; circumference of chest, 49.5 cm.; circumference of abdomen, 37.5 cm.

Stool examination was normal.

Urine examination was normal.

During this admission parathormone was given to note the effect upon the blood calcium. A basal metabolism test was done. The determined heat production was 10 per cent above the expected heat production for a three-year-old child.

October 9: The blood calcium was 10.4 mg. per 100 c.c.; the blood phosphorus was 4.4 mg. per 100 c.c.

One minim of parathormone was injected daily for three days, at the end of which time the calcium was 9.6 mg. The dosage was increased to 2 minims per day for three days. The calcium was then 10.8 mg. It was further increased to 3 minims daily for three days, and a final calcium value of 10.8 mg. was obtained.

Nov. 3, 1931 to March 23, 1932: The patient returned to the out-patient department ten times.

November 4: The weight was 13.2 kg. An acute respiratory infection was present. The blood examination revealed hemoglobin, 55 per cent; red blood cells, 2,900,000. Treatment: spleen extract was ordered to be given by mouth.

November 27: The body weight was then 12.4 kg. Blood examination revealed hemoglobin 45 per cent; red cells, 4,500,000. There was a severe cough without fever.

December 11: The cough was better. The body weight was 12.4 kg. Blood examination revealed hemoglobin, 40 per cent; red blood cells, 3,040,000.

January 8, 1932: The body weight was 12.6 kg. The general condition remained the same. Blood examination showed hemoglobin, 48 per cent; red blood cells, 2,680,000.

January 22: The blood pressure was systolic, 102; diastolic, 78. Examination of the blood showed the hemoglobin was 48 per cent. Since Oct. 21, 1931, the patient had been receiving secondary spleen extract. Today he was placed on a mixture of the secondary and of the pernicious anemia fraction of spleen, the dosage being 4 teaspoonfuls daily.

February 1: A recent head cold still existed.

February 26: Blood examination showed the hemoglobin to be 50 per cent; the red blood cells, 3,410,000.

March 11: The patient weighed 12.8 kg. The hemoglobin was 52 per cent; the red blood cells, 3,280,000.

Seventh admission was from March 23 to April 6. Blood examination showed hemoglobin, 55 per cent; red blood cells, 3,120,000; white blood cells, 48,000. The differential count showed; polymorphonuclears, 37; eosinophiles, 5; basophiles, 1; lymphocytes, 47; mononuclears, 7; degenerate cells, 8; nucleated red cells, 79 per hundred white cells.

The smear showed very marked changes in the size and shape of the red cells. Polychromatophilia, basophilia, stipling, and numerous shadow cells were found. The platelets were plentiful.

March 25: A sugar tolerance test was performed. Thirty grams of glucose were given by mouth. The following values were obtained:

Fasting:	78 mg. per 100 c.c.
½ hr.:	98 mg. per 100 c.c.
1½ hr.:	84 mg. per 100 c.c.
2½ hr.:	91 mg. per 100 c.c.
4½ hr.:	98 mg. per 100 c.c.

April 1: The plant pigments of the blood were 0.035 mg. per 100 c.c. The vitamin A content was found to be 13 units per 100 c.c.

April 4: A roentgenogram of the skull showed a definite increase of thickness, particularly in the posterior portion. Radial striations were more marked.

April 6: A sugar tolerance test was repeated. Thirty grams of glucose were given by mouth, with the following results:

Fasting:	71 mg. per 100 c.c.
½ hr.:	89 mg. per 100 c.c.
1 hr.:	91 mg. per 100 c.c.
2 hr.:	84 mg. per 100 c.c.
3 hr.:	75 mg. per 100 c.c.
4 hr.:	69 mg. per 100 c.c.

During this stay in the hospital, 10 c.c. of cortin were given daily by intramuscular injections for a period of ten days. No favorable effect upon the blood count was observed.

April 20 to June 7: Nine visits to the pediatric out-patient were made.

April 20: The weight was 13 kg.

The hemoglobin content of the blood was 52 per cent; the red blood cells, 3,500,000; the white blood cells, 35,000.

May 1: The urinary sediment examined according to the method of Rous[15] revealed no evidence of urinary siderosis such as occurs in hemochromatosis. Extralin (Lilly) (5.5 gm. = 200 gm. of liver digested with stomach) was started in doses of 2 teaspoonfuls daily.

May 18: The hemoglobin was 50 per cent.

Extralin (Lilly) (0.125 c.c. intramuscularly) was given. It was continued for several injections as follows:

May 21:	0.25 c.c.
May 24:	0.5 c.c.
May 28:	0.75 c.c.
May 31:	1.0 c.c.
June 4:	1.25 c.c.
June 7:	1.5 c.c.

Eighth Admission (June 12 to June 28): The patient was admitted because of swelling of both parotids with edema of face: diagnosis, mumps.

The blood examination revealed: hemoglobin, 5 gm.; red blood cells, 3,000,000; white blood cells, 7,400; polymorphonuclears, 37 per cent; lymphocytes, 52 per cent; mononuclears, 11 per cent; nucleated red blood cells, 7 per hundred white cells.

June 16: During convalescence a sugar tolerance curve was obtained after 25 c.c. of a 50 per cent solution of glucose were given intravenously (12.5 gm. or approximately 1 gm. of glucose per kilogram of body weight). The following values were obtained:

Fasting:	64 mg. per 100 c.c.
½ hr.:	187 mg. per 100 c.c.
1 hr.:	130 mg. per 100 c.c.
1½ hr.:	77 mg. per 100 c.c.
2 hr.:	48 mg. per 100 c.c.
3 hr.:	56 mg. per 100 c.c.

June 18: The blood serum proteins were 7.85 per cent by the refractometer method.

June 26: An x-ray examination of the skull revealed findings similar to those observed on April 4, 1932.

July 12 to December 13: Thirteen visits were made to the out-patient department.

July 12: The weight was 13.4 kg. He had been receiving fetal liver extract in dosages of 2 teaspoonfuls daily since June 28.

August 8: The blood counts were found to be hemoglobin, 46 per cent; red blood cells, 2,690,000; white blood cells, 16,000. There were 108 nucleated red cells per hundred white cells.

August 29: The plasma phosphotase was found to be 8.7 units.

September 19: A study of the blood by wet preparations for sickling failed to reveal such a tendency.

October 13: The patient fell and produced a fracture of the lower third of the left fibula. A plaster cast was applied.

October 18: The blood calcium was 10.8 mg. per 100 c.c.; the blood phosphorus, 3.8 mg. per 100 c.c.

Bone marrow extract (1 teaspoonful daily) was commenced. The blood hemoglobin was 38 per cent; the red blood cells, 3,660,000; the white blood cells, 42,250. The Schlesinger test on the urine revealed no evidence of urobilogen.

November 11: An x-ray of the left tibia revealed some new bone formations at the site of the recent fracture.

November 15: The hemoglobin value was 42 per cent; the red blood count, 3,000,000. Wet preparations of blood again revealed no evidence of sickling; marked fragmentation was now observed, however.

Ninth Admission (December 13 to December 16): The patient was brought in this time for special studies. The body measurements were length, 97 cm.; circumference of the head, 55.5 cm.; circumference of the chest, 51.0 cm.; circumference of the abdomen, 46.0 cm.

December 15: Blood volume studies were made by Dr. Alberto Hurtado. We are indebted to him for the following report:

Age, four and one-half years; body weight, 14 kg.
Red cells, 3,330,000
Reticulated red blood cells, 18.4 per cent
Hematocrit—red blood cell percentage, 25.0 per cent
Hematocrit—plasma percentage, 72.8 per cent
Mean corpuscular volume, 75 cubic microns
Mean corpuscular hemoglobin, 19.6 micromicrograms
Mean corpuscular hemoglobin concentration, 26.1 per cent
Total plasma volume, 767 c.c.
Total plasma volume per kilogram body weight, 54.8 c.c. (average, 50 cubic centimeters)
Total blood volume, 1,053 c.c.
Total blood volume per kilogram body weight, 75.2 c.c. (average, 72 c.c.)
Red blood cell volume, 263 c.c.
Red blood cell volume per kilogram body weight, 18.8 c.c. (average, 22 c.c.)
Hemoglobin per hundred cubic centimeters of blood, 6.53 gm.
Total circulating hemoglobin, 69 gm.
Total circulating hemoglobin per kilogram of body weight, 4.92 gm.
Blood viscosity, 4.0 (normal 4-4.5)

December 16: Determination of the blood lipids resulted in the following values:

Total lipids	586 mg. per 100 c.c.
Cholesterol	148 mg. per 100 c.c.
Fatty acids	438 mg. per 100 c.c.
Lecithin	179 mg. per 100 c.c.
Residual fat	245 mg. per 100 c.c.

December 17: The stool fat was 38 per cent of dry weight (normal, about 33 per cent).

January 17, 1933 to October 13, 1933: Nineteen visits to the out-patient department were made.

January 17: An acute upper respiratory infection existed. The hemoglobin was 41 per cent, the red blood cells, 2,630,000.

February 14: The weight was 13.8 kg. Bile (ox gall, Lilly), 5 grains twice daily, was now tried as a form of therapy. The blood showed hemoglobin, 42 per cent; red blood cells, 2,520,000; white blood cells, 64,000.

February 28: Blood examination revealed hemoglobin, 35 per cent; red blood cells, 2,450,000.

April 25: The hemoglobin was 38 per cent (6.6 gm.), and the red blood cells, 2,370,000.

Thymus extract, 2 grains three times daily (1 grain = 8 gm. fresh thymus), was started.

May 23: The hemoglobin was found to be 37 per cent (6 gm.), and the red blood cells numbered 3,700,000.

July 18: Swelling of the eyelids and enlarged cervical nodes were observed. The cardiac murmur had become more rough. The rate was rapid.

August 15: Ventriculin and dilute hydrochloric acid were prescribed.

September 5: The hemoglobin was now 37 per cent (5.7 gm.); red blood cells, 2,580,000. Lextron (Lilly), 1 teaspoonful three times daily, was started.

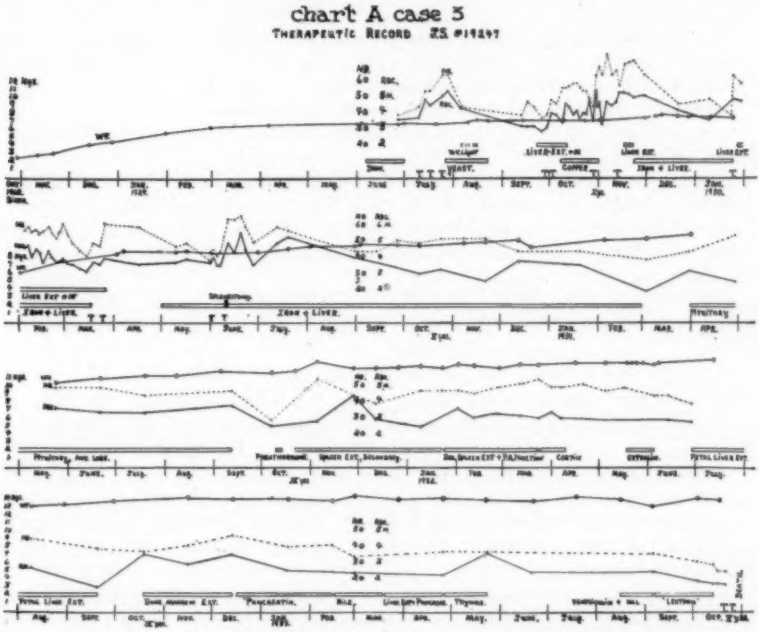

Chart A.—Case 3. Explanation of dosages. *Iron*, saccharated ferrous carbonate 0.3 gm. t.i.d.; *u-v. light*, ultraviolet rays, six treatments; *yeast*, one-half teaspoonful t.i.d.; *liver extract*, No. 55, one-half ampule daily (50 gm. liver); *copper*, 2 c.c. of 0.5 per cent solution of copper sulphate daily (0.02 gm.); *T*, blood transfusion, fifteen (total, 2020 c.c.); *iron and liver*, iron as above, liver daily in diet; *splenectomy; pituitary*, anterior lobe, 0.13 gm. t.i.d.; *parathormone*, 3 minims daily for nine days; *spleen extract*, secondary, one teaspoonful b.i.d.; *spleen extract, secondary with P. A. fraction*, four teaspoonfuls daily; *cortin* (adrenal cortex extract), 5 c.c. b.i.d. for 10 days; *extralin*, 0.125 to 1.5 c.c. daily, intramuscularly; *fetal liver extract*, two teaspoonfuls daily (150 gm. of fresh whole fetal liver); *bone marrow extract*, one teaspoonful b.i.d.; *pancreatin*, one teaspoonful daily; *bile*, 0.65 gm. daily; *liver extract* with *pancreas*, two teaspoonfuls daily; *thymus extract*, 2 grains t.i.d. (1 grain=8 gm. of fresh thymus); *ventriculin*, one teaspoonful b.i.d.; *lextron*, one teaspoonful t.i.d.

October 3: The heart was obviously enlarged. The hemoglobin was 32 per cent (4.8 gm.); red blood cells, 1,950,000; white blood cells, 30,600.

Tenth and Final Admission (Oct. 13, 1933 to Oct. 31, 1933): The patient was readmitted to the hospital because of progressive weakness, edema, and cardiac dilatation.

October 13: Blood examination showed: hemoglobin, 30 per cent (3.7 gm.); red blood cells, 1,840,000; white blood cells, 33,000. The body measurements were as follows: length, 97 cm.; circumference of head, 58 cm.; circumference of chest, 51.5 cm.; circumference of abdomen, 52 cm.

The blood typing, according to the Moss system, was found to be Group III.

October 14: The red cell volume was 14.3 per cent.

The total serum proteins were 7.29 per cent; albumin, 3.33 per cent; globulin, 3.38 per cent.

Blood lipid studies now revealed:

Total lipids	585 mg. per 100 c.c.
Phospholipid	85 mg. per 100 c.c.
Residual fat	404 mg. per 100 c.c.
Fatty acids	505 mg. per 100 c.c.

The electrocardiographic report was as follows: P-R interval, 0.15 sec.; QRS., 0.06 sec.; rate, 126; S-A tachycardia; right ventricular preponderance.

October 21: A blood culture remained sterile.

In the urine a trace of albumin and occasional casts were found.

It was evident that during this final admission the patient's condition was rapidly becoming worse.

October 29: Râles were heard throughout both lung bases, the heart dilated further, and death occurred on Oct. 31, 1933. There was some evidence of a gastrointestinal infection during the latter days of life. A stool culture at this time revealed a gram-negative bacillus belonging to the paratyphoid A group.

The clinical diagnosis was Mediterranean anemia, pericardial effusion, bronchopneumonia terminal.

AUTOPSY

J. S., white, male, aged five years, A-2414. The child died Oct. 31, 1933, at 5:30 A.M. Autopsy was performed by one of us (G. H. W.) the same day at 9:30 A.M.

Anatomic Diagnosis.—Anemia with hyperplasia of hemopoietic tissue. Abnormalities of the bony skeleton. *Pigmentation* of viscera, lymph glands, gastric mucosa, and ductless glands. Fatty degeneration of myocardium and liver. Slight bronchopneumonia. Subcutaneous edema. Hydropericardium. Laparotomy wound (splenectomy). *Thalassemia.*

The *body* was that of a somewhat emaciated Italian boy, five years old, measuring 100 cm. in length. Rigor mortis was well established. There was an old scar in the left half of the abdomen, running along the inner surface of the rectus for a distance of about 10 cm. and then laterally for a distance of about 8 cm. (splenectomy). The dorsa of the feet showed pitting edema. There was considerable edema of the face, particularly the eyelids and scalp. The eyes were completely closed by this edema. The head appeared very large. The *skin* seemed to show no abnormal pigmentation. Histologically the skin showed pigment in its basal cell layer, but its amount was not unusual, and it gave no stain for iron. The sweat glands contained no pigment. On incision, the subcutaneous fat was scant in amount and of a rather brownish yellow color. The striated muscles were decidedly pale and somewhat atrophic. The abdominal cavity contained no free fluid. There were old adhesions beneath the operative wound. The bladder contained a good deal of urine. The liver protruded several centimeters below the costal margin and was much enlarged. The spleen was absent. No accessory spleen was found. The thorax had a normal contour, and there was no evidence of beading or deformity due to rickets. The mediastinum showed very little fat. Both pleural cavities

were free of fluid. The lungs were voluminous. The pericardial cavity contained a considerable amount of clear lemon yellow fluid, about 70 to 80 cc.; no bile pigment nor urobilin was present in this fluid. The pericardial surfaces were all smooth, and there was no apparent cause for this accumulation of fluid in this cavity whereas all the other cavities were free of fluid.

The *thymus* was atrophic although it extended over the parietal pericardium for a distance of 2 to 3 cm. The thymus had a definite yellowish brown pigmentation but was very thin. The lobes were clearly marked out. Histologically the thymus showed aplasia and no deposits of pigment.

Heart weighed 160 gm. It was of normal size. The epicardium was smooth and glistening. The epicardial fat was not abundant. All cavities of the heart contained tenacious, gelatinous clots, obviously rich in fibrin. The intima throughout all cavities was smooth and normal. The myocardium of the right ventricle was a little pale, but the myocardium of the left ventricle showed a typical mottling or tigering associated with anemia and fatty degeneration. Histologically the heart muscle fibers contained a good deal of yellow granular pigment resembling the usual lipochrome pigment and commonly situated at the poles of the nuclei. Some of this pigment gave a strong reaction for iron (Fig. 1). Fine fat droplets in muscle fibers were readily stained.

Lungs.—The left lung weighed 100 gm.; the right, 140 gm. Both lungs were voluminous and similar in every respect. The bronchi contained a little mucus. The bronchial lymph glands were enlarged and somewhat pigmented, but of a definite reddish tint as though hyperplastic. One or two of them measured at least 1 or 2 cm. in diameter. The pulmonary vessels were negative. Cut section in general was a pale pinkish gray color, and the tissue was air containing. A few dark, reddish pink areas gave the impression of recent consolidation. These areas occurred here and there, some in the upper and others in the lower lobes. Histologic sections showed acute bronchitis, edema and early bronchopneumonia.

Spleen was previously removed and described by us.[22] This spleen showed the cellular type of reaction (probably early stage) as contrasted with the other spleen reported in the same paper. Pigment was fairly abundant, and some of it gave a positive test for iron.

Gastrointestinal Tract.—The esophagus was pale. The fundus of the stomach showed an intact mucosa. It had a definite golden brown tint, the mucosa being obviously pigmented and the smooth muscle very pale. The mucosa close to the pylorus was pale and smooth, unpigmented. The pylorus was normal. The duodenum appeared normal and unpigmented as was the small intestine. Peyer's patches in the ileum were somewhat enlarged but did not measure over 1 to 2 mm. in thickness. They might have been slightly pigmented, but they did not have the reddish color of the mesenteric lymph glands and appeared to differ sharply from the body lymph gland tissue in this respect. The appendix was normal. The large bowel showed a pale, nonpigmented mucosa and easily seen but not enlarged solitary follicles. The rectum was normal. Histologically the stomach showed a normal structure but for pigment granules in the epithelium of the acini deep in the mucosa (see earlier paper[22] for illustration, *Fig. 3*). This pigment gave a strong test for iron and was found in the chief cells not in the acid cells. This pigment was not found in the mucosa of the duodenum. Brunner's glands showed a little pigment which gave a faint stain for iron. The mucosa of the jejunum and ileum was normal and pigment-free, but Peyer's patches showed small amounts of yellow granular pigment. Some of this might stain for iron. Appendix showed a slight inflammatory reaction. Colon showed normal mucosa and solitary follicles with no pigment.

Pancreas was a little enlarged and rather firm. The lobulation was regular. It had the color of maple sugar, a deep buff color as noted in the other cases. Histologic sections showed much pigment in the pancreatic acinar cells particularly

adjacent to islets but not in the islet epithelium. This pigment all gave a strong blue reaction to the iron stain. Many acini were free from iron deposits, and some contained fine granules only, but many contained large coarse pigment granules, and some epithelium appeared to be degenerating because of large pigment deposits. There was no increase in stroma (see characteristic illustrations in our first paper,[22] *Figs. 4 and 5*).

Liver weighed 810 gm. It was definitely enlarged. The capsule was transparent, and through it could be seen the deep reddish brown parenchyma. This appearance was identical with the other cases of this type and indicated considerable pigment deposit. The consistency of the liver was normal. Lobulation was regular. There was some central yellowish tinting of the dark brownish color of the lobules. The *gallbladder* contained rather thin, brownish bile. The mucosa of the gallbladder had a pale brown tint after washing. The biliary passages were pale and normal elsewhere. There was bile present in the duodenum. *Chemical analysis* of the liver parenchyma showed 292 mg. Fe per 100 gm. fresh tissue. Histologic sections showed heavy pigment deposits in the hepatic epithelium particularly in the marginal half of each lobule. This pigment in the marginal half of the lobule gave a positive iron stain, but in the central half the pigment did not stain strongly for iron. The granular pigment was conspicuous in the Kupffer cells and did not stain for iron. The central half of the lobules showed large fat droplets in the liver cells and occasional focal necroses. There were no marrow cells seen in the lobules, but about the bile ducts were occasional nests of mononuclear cells. The *gallbladder* showed pigment granules in the epithelium and also in the submucosa especially at the crests of the folds. This pigment was negative by iron stains.

Kidneys.—The left kidney weighed 120 gm.; the right 120 gm. They were perhaps somewhat enlarged. The capsules stripped off easily, leaving a pale brown surface. On section the cortex measured 6 mm. in thickness. The striations were perfectly regular. Cut section seemed to have a definite pale brown pigmentation throughout. The glomeruli were hard to see. The pyramids were very pale. The pelves were normal. Chemical analysis of the kidney parenchyma showed 3.9 mg. Fe per 100 gm. fresh tissue, which is a low normal content. Histologic sections showed normal glomeruli and stroma. Many of the convoluted tubules showed epithelium which contained fine or coarse pigment granules which did not stain for iron. Occasionally one found a tubule which contained in its epithelium fine pigment granules giving a positive stain for iron (Fig. 2). The patchy distribution of this pigment was difficult to understand, but it explained the brown color of the renal cortex noted in gross. Casts were present in a few tubules.

Pelvic Organs.—The prostate was small and pale and appeared to be normal grossly. Histologically there was no pigment. The bladder mucosa was pale and nonpigmented. The epididymes were pale and white. *Testes* were definitely pigmented and showed a dark brown color. Histologically the *testis* showed much coarsely granular yellow brown pigment in the interstitial tissue. This pigment did not stain for iron nor hemofuscin. The immature tubules showed no pigment, nor did the endothelium of the blood vessels and capillaries.

Ductless Glands.—The *adrenals* were perhaps a little smaller than normal. They were normal in outline and measured $3.5 \times 2 \times .75$ cm. On section the outer part of the cortex was thin, yellow, and opaque in contrast to the thicker inner brown portion. The medulla, where it appeared, was a pale milky color. The cortex seemed to have a definite brown pigmentation. Histologic sections showed small amounts of an iron-containing pigment in the cells of the glomerular zone of the cortex (compare Fig. 6 from another case). There was much pigment that did not stain for iron. Fat stains showed abundant fat droplets in the cortical cells. The structures in general were normal.

The *thyroid* appeared to be of normal size. It was removed after injection of formalin. It had the usual reddish brown color, but the brown was a little more conspicuous than in the normal thyroid. Lobulation was normal. The *parathyroids* were difficult to find. Histologic sections showed large amounts of iron-staining pigment in the majority of the acinar epithelial cells in the thyroid. No pigment appeared in the colloid (see Fig. 5). There was no fibrosis. Parathyroids (two) appeared to be normal and showed no pigment.

The *hypophysis* was definitely small and the sella turcica shallow. The stalk was well marked. It was pale. Histologic sections showed no pigment and a normal structure.

Vascular system was perfectly smooth and elastic throughout all large vessels. Tenacious clots could be pulled from a great many of the veins, even from the coronary veins. *Striated skeletal muscles* were normal and contained no pigment.

Lymphatic System.—The absence of the spleen might account in part for the enlargement of the lymph glands, which was a conspicuous feature in the autopsy. The lymph glands in the mediastinum and about the bronchi had an appearance much like that of the spleen. Enlarged lymph glands in the neck and retroperitoneal region might have this reddish tint but again might have a conspicuous reddish brown color. Some of the larger ones measured from 1 to 1.5 cm. in long diameter. They appeared to be rather moist and somewhat congested, although it was more the appearance of blood in the sinuses than of congestion of the capillaries of the gland. The lymph glands about the pancreas were conspicuously enlarged; some of them were brown in color, while others had a slight greenish brown cast, perhaps this pigment being added from the liver and pancreas. The lymph glands in the fan of the mesentery and along the large bowel were conspicuously enlarged. Most of these were of a distinct reddish color or had a reddish brown staining against the pale watery fat. Histologic sections showed much uniformity. The architecture was well preserved, and there was no chronic inflammation and fibrosis. The germinal follicles were large, active looking and nonpigmented. The sinusoids were filled with fluid and wandering cells. Red blood cells were numerous in many sections. *Pigment* was conspicuous, and much of it gave a positive iron stain. Some of the large pigment grains were a bright yellow and might give a positive stain for hemofuscin, but much of the pigment gave no reaction to any specific stains. Marrow metaplasia was noted occasionally, and some sections showed large nests of myelocytes, nucleated red cells and megakaryocytes. Occasional nests of foam cells, as described in spleen and marrow, were found (Fig. 4).

Skeletal System.—The skull cap was greatly thickened, and, when the scalp was turned back, it presented a definite mulberry color as though bone marrow was just beneath the periosteum. The *calvarium* was enormously thickened, the thickness ranging from a fraction of a centimeter up to 2 cm. In places the radial markings due to bone spicules and showing in the x-ray stood out clearly. The bone marrow between these trabeculae had a definite chocolate red color. This change seemed to involve all parts of the calvarium, tapering off to the thin temporal bones. In spite of the fact that this bone looked rather soft and porous, it contained a good deal of structural bone and could not be cut with the knife. The base of the skull appeared to be normal. All of the venous sinuses were clear and contained tenacious postmortem clots. The *ribs* were enlarged in places, as described in other cases, but this fusiform enlargement did not involve the portions of the ribs close to the costochondral junctions but the part of the rib close to the tubercle. This has been described in other clinics. This was particularly true in the upper six or eight ribs. The lower three ribs showed involvement of the inner two-thirds. It appeared that the bone marrow filled all the spaces and really replaced most of the outer bony shell, filling up all spaces right up to the periosteum. In spite of this, the rib cut with some difficulty although it had not the toughness of normal rib.

The rib marrow had the same chocolate, dark red color as noted in the calvarium. *Chemical analysis* of the rib showed 33.5 mg. Fe per 100 gm. fresh weight, which is within normal limits. The bones of the *vertebrae* showed the same colored bone marrow, and the trabeculae were inconspicuous; the bones cut with only moderate difficulty, indicating definite thinning of the trabeculae. The shaft of the femur in its middle third was greatly thinned, measuring 1 mm. in thickness. All of the space inside of this shell was filled with dark cellular, chocolate, red bone marrow, but there was no deposit of this marrow between the periosteum and the shaft. Histologically the bony trabeculae were thinned, but there was no apparent overactivity of the osteoclasts. In the ribs the red marrow was found between the shaft and the periosteum, and in the calvarium the marrow actually invaded crevices in the periosteum. The *red marrow* presented a considerable variety in ribs, vertebrae, long bones, and calvarium. The marrow was very cellular, and few fat cells remained anywhere. Nests of parent marrow cells were conspicuous as were nucleated red cells and myelocytes. Phagocytes were found in moderate numbers, and some contained iron staining pigment. Megakaryocytes appeared in goodly numbers. Some parts of the marrow showed some fibrosis, and there were islands of foam cells, which might attain a considerable size. These groups of foam cells were usually in the marginal portion of the bone and close to trabeculae. This change was illustrated in our first paper,[22] ***Fig. 7.***

Brain weighed 1280 gm. The dura was not thickened nor pigmented but was somewhat adherent to the calvarium. The pia arachnoid over the brain was delicate, and the brain appeared quite pale and normal in all respects. On section the brain was normal, and the choroid plexus was not pigmented.

CASE 4.—Auburn City Hospital (Dr. C. H. Maxwell), No. 9272.

History.—M. D., an Italian boy, five years and ten months old, developed an acute upper respiratory infection on Jan. 17, 1932. When examined, he was found to be extremely ill. The temperature was 104° F. The respirations were rapid. The pulse was rapid and weak. He was markedly anemic. The skin was of dull yellowish tint. The head revealed some bossing, but only suggestive mongoloid features were observed.

The heart was somewhat enlarged. A loud blowing systolic murmur was audible over the entire precordium. Many crepitant râles were heard over the lung bases. The percussion note was unimpaired. The abdomen was distended and ascites was present. The spleen reached the crest of the ilium. The liver was palpated four fingerbreadths below the costal margin. The legs were edematous. He grew rapidly worse and expired on the fourth day of illness.

The past history revealed that birth had been of a normal spontaneous type. The birth weight was 4 pounds. He was one of twins, the other child weighing 5 pounds at birth. He was breast fed for two months, then was given a formula for eighteen months. Development was slow. He walked and said simple words at eighteen months. The first tooth erupted at fourteen months. He gained weight slowly and took food poorly.

The liver and the spleen were found to be enlarged while he was still a small infant. He had been in the Auburn City Hospital on three different occasions for the treatment of anemia, poor appetite, mild respiratory infections, mumps, nosebleeds, and other minor conditions. During one of these admissions (Jan. 21, 1931) it was noted that the facial expression was sad and pale. Edema of eye lids existed. The teeth were good. The tongue was coated. The tonsils were slightly enlarged. The head circumference at this time was 47 cm.; the chest, 56 cm. The lungs were normal. The heart was enlarged with the apex in the seventh intercostal space. A loud systolic murmur was heard. The abdomen was large and protuberant with prominent superficial veins. The spleen was very large and hard.

The father and mother and ten other siblings constituted the family. A twin brother and a two-year-old brother suffered from the same type of anemia. There was no evidence of other types of familial illness within the family.

The observations on the blood are reported in Table I.

TABLE I

DATE	HEMOGLOBIN (%)	RED CELLS	WHITE CELLS	POLYMORPHONUCLEARS (%)	LYMPHOCYTES (%)	MONONUCLEARS (%)	NUCLEATED RED CELLS PER HUNDRED WHITE CELLS
1/27/31	33	2,680	57,300	51	37	6	115
3/25/31	46	2,480	44,600	55	41	3	130
4/ 2/31	40	3,700	10,300	40	49	7	20
7/24/31	35	2,690	14,150	51	44	5	43

The stained smears revealed marked variations in the size and shape of the red blood cells. The platelets appeared plentiful.

The icteric index was 9 units. Fragility of the erythrocytes to hypotonic salt solution showed hemolysis to begin at the concentration of 0.30 per cent and was complete at 0.20 per cent. The urine was dark in color and showed a trace of albumin.

AUTOPSY

M. D., Italian, male, aged five years, A-1728. The child died Jan. 20, 1932, at 10:00 P.M. Autopsy was performed by one of us (G.H.W.) Jan. 21, 1932, at 10:00 A.M.

Anatomic Diagnosis.—Anemia, with hyperplasia of hemopoietic tissue. *Pigmentation* of viscera, ductless glands and lymph of glands. Abnormalities of bony skeleton. Enlarged liver and spleen. Infarcts of spleen. Hypoplasia of adrenals. Organizing bronchopneumonia and edema of lungs. Fatty degeneration of liver and myocardium. *Thalassemia.*

The body was that of an Italian boy, 42 inches tall. Rigor mortis was slight. Livor mortis was absent. The skin had a peculiar pigmentation, somewhat the color of a Chinese. The face had a definite mongolian cast, and the frontal bosses were slightly conspicuous. The hair was black and curly, the eyes, brown. The pupils were equal. The thorax was symmetrical; the abdomen, greatly distended. No hemorrhages were observed over the skin. The subcutaneous fat was scant and pale yellow in color. The striated muscles over the thorax and abdomen were decidedly pale and watery appearing. There was some subcutaneous edema over the lower legs. The peritoneal cavity contained a great excess (probably about 1000 c.c.) of clear, lemon yellow fluid. The surfaces were everywhere smooth and moist. No hemorrhages were noted. The omentum showed very little fat. It was normally disposed. The liver extended well below the costal margin. The lymph glands were everywhere conspicuous. The bladder was full of clear urine. Both pleural cavities were clear. The lungs were voluminous. The pericardial cavity contained a considerable excess of lemon yellow fluid. The pericardial surfaces were smooth.

The *thymus* showed two lobes, coming down to the base of the heart, measuring 2 and 4 cm. in length by 1.5 to 2 cm. across, and about 0.5 cm. in thickness. The tissue was normal histologically, and no pigment was noted.

Heart weighed 71 gm. It was about normal size for a child of this age. The epicardial surfaces were normal. The epicardial fat was scant. The endocardium and valves throughout were normal. The right ventricle contained well-formed antemortem clots. The chambers were dilated. The myocardium was pale reddish brown in color with perhaps more brown pigmentation than normal. There was no mottling with fat, but the muscle was distinctly pale. Histologically the heart

sections showed edema. There was much pigment in the heart cells at the poles of the nuclei. This pigment was in fine grains and much, but not all, of it gave a strong test for iron (Fig. 1).

Lungs.—The left weighed 170 gm.; the right, 226 gm. They presented an identical picture. The glands at the hilum were conspicuous, and most of them were moist and pink, but some contained coal pigment. The bronchi contained a smooth velvety mucosa and were filled with frothy serum. The vessels were normal. On section, the lung tissue was very wet and dripped fluid. In places the lung tissue looked glassy and semitranslucent because of this fluid. Other areas were pale and normal. Posteriorly in the lower lobe was a definite area of bronchopneumonia, measuring 3 or 4 cm. in its greatest diameter. Here the lung tissue was gray, granular, and moist. Histologic sections showed the usual picture of a bronchopneumonia but with early organization in some areas. There was much edema but no abnormal pigment.

Spleen weighed 420 gm. It was enormously enlarged, measuring about 15 cm. in its long axis. There were adhesions over its anterior surface. The capsule in general was transparent, but there were irregular areas of opacity showing beneath the capsule, some of which lay beneath the adhesions mentioned. These *infarcts* presented a very irregular border, separating the opaque tissue from the normal splenic pulp. Some of these borders showed a greenish translucency, suggestive of many wandering cells. The larger infarcts measured 2 cm. in their long dimension. Some of these infarcts were indefinite as to outline, merging into the splenic pulp. These were less opaque than the others described. They made up perhaps one-seventh of the total bulk of the spleen. Section elsewhere showed a uniform fibrous spleen, presenting a glassy cut surface. The organ was very rubbery. There was no exceptional pigmentation. The cut section was a dull pinkish red. The connective tissue was obviously much increased and the malpighian bodies were obscured. Trabeculae were inconspicuous, because of the diffuse connective tissue increase. *Chemical analysis* showed 16 mg. iron per 100 gm. fresh weight which was less than normal or a low normal amount. Histologic sections of this spleen, in contrast to that in Case 3, showed a much more chronic process. There was much more fibrosis of the pulp, and the various pulp cells were obscured. Pigment in moderate amounts was seen in phagocytes and endothelial cells of the sinusoids. Some of this pigment gave an iron stain. The trabeculae might show occasional deposits of iron and calcium. Malpighian corpuscles were small and hard to find. There was little marrow metaplasia. The infarcts presented the usual picture.

Gastrointestinal Tract.—The esophagus was normal. The *stomach* contained partially digested food and was coated with mucus. Its mucosa had a definite brownish tint which was most marked in the cardia and faded close to the pylorus to a very pale brown. No hemorrhages were noted. The pylorus was normal. The *duodenum* showed only a very faint tint of brown. The jejunum shows a nonpigmented mucosa. The solitary follicles were easily seen and measured about 1 mm. in diameter. In the ileum the solitary follicles were conspicuous, some of them measuring about 2 mm. in diameter. Peyer's patches were rather conspicuous, and the follicles were easily made out. The appendix showed some postmortem slaty staining. The large bowel showed scattered solitary follicles, 1 to 2 mm. in diameter. No pigmentation was noted. There were no ulcers. Histologic sections showed abundant iron-staining pigment in the acinar cells of the gastric mucosa. The chief cells contained most of this pigment, but the acid cells did contain some fine pigment granules. The muscle coats contained no pigment. Duodenum contained no pigment in its mucosa but *Brunner's glands* contained liberal amounts of fine granular yellow pigment which stained for iron. Jejunum, ileum, and colon

showed no pigment in mucosa or muscle coats. Peyer's patches and solitary lymph follicles showed an occasional granule of iron-staining pigment contained in a phagocyte. This was a replica of Case 3.

Liver weighed 1175 gm. It was enlarged. It was very deeply pigmented, having a dark buff color. The capsule was smooth, and through it the lobules could readily be seen. The consistency was normal. The architecture was regular. The lobules showed a peripheral translucent brown zone and a central opaque yellow spot which was undoubtedly fat. There was no increase in the periportal tissue. The pigmentation of the organ was as definite as is observed in hemochromatosis. *Chemical analysis* showed 114 mg. iron and 22 mg. copper per 100 gm. of fresh tissue. The *gall bladder* contained a little yellow bile and showed postmortem staining. The mucosa was perfectly smooth and normal. Histologic sections showed abundant large fat droplets in the center of the *liver* lobules. These central liver cells contained little pigment, and much of it did not stain for iron. Kupffer cells contained relatively little pigment, and most of this did not give an iron stain. The marginal liver cells close to the portal tissues contained heavy deposits of a yellow pigment containing iron. There were occasional nests of marrow cells in the capillary spaces in the liver lobules—an evident marrow metaplasia of moderate grade. Perhaps this change might compensate somewhat for the lack of marrow metaplasia in the fibrous spleen in this case. *Gallbladder* mucosa showed no pigment.

Pancreas was about normal in size and quite firm in consistency but very deeply bronzed—as dark as the liver—a dark maple sugar color. The lobules were distinct. The stroma was slightly edematous. Histologic sections showed a pancreas which was a replica of that gland in Case 3 and need not be described.

Kidneys.—Each weighed 100 gm. They were slightly enlarged. The capsule stripped readily leaving a very pale surface which had a faint brownish yellow color. On section the cortex was about 5 mm. in thickness. The striations were well preserved. The contrast between the brown cortex and the pinkish gray pyramids was conspicuous. The pelves and ureters were normal. Histologic sections showed normal structures. There were abundant fat droplets in the epithelium of the convoluted tubules. Pigment deposits were infrequent but picked out occasional tubules where they might be conspicuous. Henle's tubules were often involved. Some of this pigment stained for iron (Fig. 2).

Pelvic Organs.—The bladder was normal. No pigmentation was noted. The *prostate* was very small. Histologically it was normal, and no pigment was found. The *testes* were infantile in type. On section they presented a pale brownish color. Histologic sections showed the usual peculiar distribution of pigment. The immature tubules in the testis showed no pigment, but the interstitial tissue showed some yellow coarse pigment which contained no iron. In the endothelium of the capillaries were a few fine pigment grains which stained for iron. Epididymis was normal. The striated voluntary *muscle* was pale and moist in gross. Histologically the muscle fibers were normal. A few capillaries were found in which endothelial cells contained fine granules of iron-staining pigment. The blood vessels appeared perfectly normal. There was no pigment noted in the walls of arterioles in various organs and tissues.

Adrenals were distinctly smaller than normal and hypoplastic. The right measured 10 to 15 by 3 mm. The medulla was conspicuous. The cortex was very thin, measuring less than 1 mm. in thickness and showed a slight amount of brown pigment. The other adrenal presented about the same appearance. Histologically this adrenal was a replica of that in Case 3 (Fig. 6).

The *thyroid* was small. On section it showed a dark brown color. Colloid was obviously present. There was no question about the increase in the brown pigmentation. Histologic sections showed a very large amount of iron-staining pigment

(Fig. 5). Practically every epithelial cell in every acinus contained these fine pigment granules which were located in the colloid side of each cell but not in the colloid. The thyroid was very cellular and poor in colloid which stained faintly. There was no increase in stroma.

The *hypophysis* was normal in gross and showed some brown pigmentation. Histologically the structures of the hypophysis were normal. A few grains of pigment were seen in the protoplasm of the acidophile cells, and some of this stained sharply for iron.

Lymphatic System.—The lymph glands about the pancreas were large, a dull pink in color, and moist. Some of them contained a good deal of brown pigment, and others looked much like the spleen. The larger ones measured 1 cm. in diameter, and a great many smaller ones 2 to 4 to 6 mm. in diameter found close to the spleen, about the duodenum, and in the gastrohepatic omentum. The mesenteric glands were all conspicuous. They were a very faint pinkish gray color with a slight brownish tint and were moist and swollen. Some measured over 1 cm. in diameter. Conspicuous lymph glands were noticed in the thorax. Some of them appeared pink and moist; others appeared to contain brown pigment, and still others, a mixture of brown pigment and a little coal pigment. The retroperitoneal glands had the same general appearance but contained more of the brown pigment. Histologically these various lymph glands presented the same findings as described in Case 3. Metaplasia was conspicuous in some sections, and true bone marrow activity was seen. Foam cells appeared rarely but were often noted in association with the marrow cells (see Fig. 4). Phagocytes were frequent and some contained many red cells as well as pigment. The lymph glands appeared to be as active as the spleen in this case.

Bone Marrow.—The ribs did not show any unusual thickenings. On section, the bone marrow had a definite rusty red color. It was uniform. The bodies of the lumbar vertebrae showed a dark brownish red marrow thoughout. These bones contained delicate bony trabeculae. The shaft of the *femur* appeared to be definitely thin and was quite easily cut and split. The bone marrow was dark brownish red in color and cellular throughout. Histologic sections showed that this *marrow* was exactly like that described in Case 3, and by other observers. Phagocytes containing iron-staining pigment and even red cells were found occasionally but were not conspicuous. Foam cells were observed in small clusters but were less conspicuous than usual. The marrow hyperplasia was observed between the rib shaft and periosteum.

Brain weighed 1200 gm. Section through the calvarium showed it to be thin and normal except over the frontal region where the outer and inner tables were separated for a distance of about 8 or 9 mm. There was present characteristic bony hyperplasia in this region. A similar change was seen over the occipital region but was less conspicuous. The meninges were all clear, moist and normal. The brain appeared normal on section. The pineal gland appeared to be normal. The *choroid plexuses* showed a definite rusty brown pigmentation. The choroid histologically contained a good deal of coarsely granular yellow pigment staining negatively for iron within phagocytes in the areolar tissue below the epithelium of the plexus. A little of the same sort of pigment was noted in the epithelium. No hemosiderin was found.

CASE 5.—No. 22501 (Dr. J. M. Parker).

History.—John S., an Italian boy two and one-half years old, was admitted to the Strong Memorial Hospital on June 8, 1930.

At one year of age the patient developed an acute upper respiratory infection with fever. A mass, which the physician identified as an enlarged spleen, was

noticed at this time by the mother. Pallor, weakness, and failure to gain weight developed soon and led to his admission to the hospital.

The birth, which was normal, followed a full-term pregnancy. The weight was 9½ pounds. He was breast fed for nine months and was then placed upon the usual infant diet. Cod liver oil was not given until he was two years old, and orange juice was given irregularly during infancy.

Dentition, speech, and muscular development were normal.

Frequent head colds, pneumonia at six months, and measles at two years had occurred.

The father, forty-two years old, the mother, thirty-six years old, and a brother, six years old, were normal.

Physical Findings.—Essential features were the prominent bosses of the head and facies suggestive of the mongoloid type. Pallor and puffiness of the eyelids and cheeks were present. The tonsils and cervical lymph nodes were enlarged. The heart was slightly enlarged and revealed a soft systolic murmur. The abdomen was prominent and contained a markedly enlarged, hard spleen which extended to the iliac crest. The liver border was palpated from three to four fingerbreadths below the costal margin.

Laboratory Findings.—Blood examination showed hemoglobin, 48 per cent; red blood cells, 2,960,000; white blood cells, 19,840. Only a few nucleated red cells were present, but the morphology of the cells was identical with that usually seen in Mediterranean anemia. The blood calcium was 8.5 mg. per 100 c.c.; phosphorus, 5.3 mg. per 100 c.c.; plasma protein, 8.7 per cent; serum chlorides, 485 mg.; non-protein nitrogen, 96.3 mg. The blood lipids showed: plasma, total lipids, 550 mg. per cent; cholesterol, 112; fatty acids, 438.

The urine contained 18 to 25 red blood cells per high powered field, and a few hyaline and granular casts.

The clinical impression was Mediterranean anemia, and it was suggested that the hematuria was the result of acute nephritis.

Course.—After an intravenous blood transfusion, the patient returned to the private care of Dr. J. M. Parker, to whom we are indebted for the opportunity to study the case in detail.

During the period from April, 1933, to July 4, 1934, when death occurred at the age of seven and one-half years, the patient was admitted upon three occasions to the Rochester General Hospital, where further observations were made and several blood transfusions were given.

Edema with pericardial and peritoneal effusions developed during the latter months of life. The weight increased from 55.5 pounds to 68 pounds during the last month.

Representative blood counts were:

April 27, 1933 (First admission): hemoglobin, 37 per cent; red blood cells, 1,580,000; white blood cells, 8550; neutrophiles, 14; mononuclears, 62; many nucleated red blood cells.

May 27, 1933 (one week before death): red blood cells, 3,580,000; white blood cells, 6,450; neutrophiles, 51 (juvenile forms, 5; stabs, 11; segmented forms, 35); mononuclears, 49; nucleated red blood cells, 31 per 100 white cells.

Hemolysis to hypotonic salt solutions began at the concentration of 0.42 per cent and was complete at 0.28 per cent (normal control, 0.42 to 0.32 per cent).

The x-ray studies of the long bones revealed thinning of the cortex and coarse trabeculation near the diaphyseal end. The bones of the vault showed marked porosity with thinning of both tables and with new bone laid down at right angles to the outer table.

AUTOPSY

John S., aged seven years, Italian parents; No. 89659. Autopsy was performed at the Rochester General Hospital by Dr. Istvan Gaspar. We are indebted to Dr. Gaspar for materials and permission to report this case.

Anatomical Diagnosis.—Anemia with hyperplasia of hemopoietic tissues. Splenomegaly. *Pigmentation* of viscera, ductless glands and lymph glands. Abnormalities of bony skeleton. Hypoplasia of adrenal glands. Fatty degeneration of heart and liver. Bronchopneumonia. General anasarca. *Thalassemia.*

The *body* was that of a young white boy showing excessive generalized anasarca. His eyelids, cheeks, lips, and neck were markedly edematous. Gums were anemic. Post mortem lividity was evidenced in the region of the neck and pelvis. About the face and the neck some petechial hemorrhages were noted, some of which were confluent. Scrotum and dependent portions were very edematous. The skin was of a yellowish icteric hue. *Abdomen* was distended and dome shaped. On incision a yellowish turbid fluid gushed out. No indication of peritonitis was seen. Approximately 4000 c.c. of this fluid was present. The pleural cavities were filled with fluid, yellowish in color and turbid in character. The right pleural cavity contained 200 c.c., the left contained 500 c.c. No adhesions of the pleura were noted. The pericardial sac was dilated and contained from 400 to 450 c.c. of transparent fluid. No inflammation of pericardium was seen.

Heart was hypertrophied, weighing 270 gm. Right ventricle was from 8 to 9 mm. thick, left ventricle, 11 mm. Myocardium was pale in color. Valvular constituents were normal. Histologic sections showed normal muscle fibers with little pigment at the poles of the nuclei. Only rarely did one see a pigment granule which stained for iron.

Lungs.—The right and left were of essentially the same character. Grossly no evidence of inflammation was seen. The left lung weighed 175 gm., the right lung, 240 gm. Histologically there were small areas of bronchopneumonia, some of which were of the interstitial type. Some phagocytes in the alveoli contained pigment which stained for iron. Occasional mucous glands in the mucosa of large bronchi contained pigment, some of which was hemosiderin. This pigment in the epithelium of the glands was largely in the central half of the acini close to the lumen. The blood vessels showed no pigment in the muscle coats.

Spleen was tremendously enlarged and weighed 800 gm. Externally it was of a bluish green color. The cut section was a dark red. Histologic sections gave a picture midway between the very cellular spleen (Case 3) and the chronic fibrous spleen (Case 4). There was considerable increase in interstitial stroma, and the sinusoids stood out conspicuously. The trabeculae were conspicuous, and occasionally one found deposits of hemosiderin in the crevices of the trabeculae. Hemosiderin was not readily found but was present in occasional phagocytes and rarely in endothelial cells of the sinusoids. Other yellow pigment giving negative stains for iron was found in occasional cells. The *marrow* cells were well represented, and one found many small nests of parent stem cells, abundant myelocytes, and nucleated red cells. Megakaryocytes were rare. Malpighian bodies were very small and inconspicuous. *Chemical analyses* showed 30 mg. iron per 100 gm. of fresh tissue, not far from a normal value, for the spleen.

Lymph Nodes.—The peribronchial, peritracheal, mesenteric, and mediastinal nodes were much enlarged and dark brown in color. Histologic sections showed increase in stroma in these lymph glands. Edema was conspicuous and the sinuses often contained red cells as well as wandering cells. Hemosiderin and iron-free pigment were present in many glands usually in phagocytes. Marrow cells were found in some glands but not in all. The lymph germinal follicles appeared active and normal.

Liver was markedly enlarged and of a peculiar brownish hue, and it weighed 2550 gm. The *gallbladder* contained a yellow brown colored bile which stained the mucosa brown. The bile ducts were normal. *Chemical analyses* showed a very high content of iron—395 mg. per 100 gm. of fresh tissue. Histologic sections showed an unusually heavy deposit of hemosiderin in the liver cells in the margin of the lobules. Some liver cells were so filled with hemosiderin as to show evidence of degeneration, and in fact there was some stroma increase in the portal tissues, which increase was probably related to this pigment deposit, as is seen in hemochromatosis. The Kupffer cells contained little pigment, and this was usually negative for iron. The bile ducts were normal, and bile canaliculi contained no pigment. There was some marrow metaplasia with scattered nests of marrow cells within dilated capillaries. The liver cells in the centers of the lobules appeared relatively normal and contained only a little hemosiderin.

The *stomach* mucosa showed nothing except postmortem autolysis. The *intestines* showed redness, cyanosis, and edema in the region of the duodenum and jejunum. Histologic sections showed a heavy deposit of hemosiderin in the acini cells of the gastric mucosa. There was postmortem autolysis. Duodenum showed a light deposit of hemosiderin in Brunner's glands and occasional granules of hemosiderin in the stroma of the tips of the villi.

Pancreas weighed 30 gm., and was of a peculiar yellowish brown coloration. Histologically there was postmortem autolysis, but a heavy deposit of hemosiderin was evident at a glance. Most of the hemosiderin was within acinar epithelium and in acini close to the islets. Occasionally an islet showed a few grains of hemosiderin within its epithelium.

Kidneys were definitely enlarged. The capsules stripped with ease. There was no deposition of pigment. Right kidney weighed 280 gm., left, 210 gm. *Chemical analyses* showed normal values for the kidney—4.6 mg. iron per 100 gm. of fresh tissue. Histologic sections showed normal structures. Occasional tubules showed a deposit of hemosiderin in the epithelium (Fig. 2). Other tubules showed a yellow pigment which was iron free. *Testis* histologically showed the usual pigmentation. Iron-free pigment was abundant in the interstitial tissue and appeared in large yellow granules. It also appeared in fine grains in the epithelium of a very few acini. Hemosiderin appeared in fine grains within the endothelium of many capillaries (Fig. 3).

Suprarenals were atrophic, the capsule thinned, and pigmentation increased. Histologically the glomerular zone of the cortex showed abundant deposit of hemosiderin within the adrenal epithelium (Fig. 6). Other tissues were normal.

Thyroid.—Externally the gland was of normal appearance. The pyramidal lobe was well developed and plainly visible on dissection. No manifest pathology was seen grossly. Histologically the picture was like that described in Cases 3 and 4. Fine granules of hemosiderin were abundant in the epithelium of the acini (Fig. 5).

The *vascular system* was normal in gross. Histologically many arterioles in the mesentery and kidneys showed a finely granular yellow pigment negative for iron in the smooth muscle coats. Many arterioles in the thyroid, adrenal, and mesentery contained some granules close to the elastica interna which stained for iron, and in some vessels the elastica interna in places took a deep blue iron stain.

Bone marrow was considerably increased and was of a peculiar brownish red hue. The color resembled somewhat that of the bone marrow in pernicious anemia. The bone shafts were considerably thinned. Portions of the ribs and the right femur presented similar pathology. Histologic sections were in general like those from Case 3. Hemosiderin was not abundant, but granules were found in phagocytes and occasional endothelial cells. Foam cells were rarely seen. The usual cellular hyperplasia was conspicuous.

CASE 6.—(M—i) This histologic material was sent to us through the courtesy of Dr. T. B. Cooley and supplements the material described above.

Heart.—Stains for iron were unsatisfactory.

Thymus showed aplasia but no pigment.

Spleen showed only a slight stroma increase and a cellular pulp. The malpighian bodies were normal. Iron-staining pigment was fairly abundant in phagocytes. There was relatively little marrow metaplasia in the single section studied.

Lymph glands showed abundant pigment, some of which gave a positive stain for iron.

Liver showed a heavy deposit of yellow pigment, most of which gave a positive iron stain. This pigment was very largely within the liver cells, but a little appeared in the Kupffer cells. There was a definite increase of wandering cells in the portal tissue.

Pancreas showed a heavy deposit of iron-staining pigment in the epithelial cells of the acini. Rarely a little hemosiderin was found in the islet epithelium.

Kidney showed no hemosiderin but some yellow granular pigment in the epithelium of a few tubules.

Marrow showed the usual picture of hyperplasia. Occasional foam cells were observed, and fibrosis was noted in some sections.

CASE 7.—(P—e) This histologic material was sent to us through the courtesy of Dr. T. B. Cooley.

Heart showed negative iron stains.

Thymus showed aplasia but no pigment.

Spleen in general was rather cellular, but the section was unsatisfactory.

Lymph glands examined contained only a little pigment.

Liver showed a heavy pigment deposit within the liver cells, especially in the margins of the lobules. Much of this pigment was noted in the Kupffer cells. Scattered focal hyaline necroses were found.

Pancreas presented the usual pigmentation with hemosiderin. There seemed to be a moderate increase in stroma.

Adrenal showed a faint stain for iron in the glomerular zone (compare Fig. 6).

Marrow showed the usual hyperplasia. There were sizeable islands of foam cells noted here and there as well as a little fibrosis.

CASE 8.—(No. 57332.) *History.*—E. S., an Italian girl, four years old, was born Feb. 5, 1932, by breech delivery after a twin sister, M. S., had been delivered spontaneously by vertex presentation. The obstetric record indicated that they were single ovum twins, only one placenta having been described. Nevertheless, the physical features are now so dissimilar (Fig. 7) that they are considered not to be identical twins. At birth the measurements were: length, 49 cm.; head circumference, 32 cm.; chest circumference, 31 cm.; weight, 2270 gm. On the twelfth day the weight was 2810 gm. Breathing was spontaneous. At the time of discharge from the nursery nothing abnormal was noted except that she was undersized.

When she was eight months old, pallor was noted. She became less active and more pale until eighteen months of age, when a lump was noticed in the left upper part of the abdomen. At nineteen months she was admitted to the pediatric service of the Rochester General Hospital and there received eleven transfusions during a period of nine months. Copper and iron were also administered.

At two and one-half years of age, she was admitted to the pediatric service of the Strong Memorial Hospital on July 30, 1934.

The first tooth appeared at five months. She sat at ten months, talked at one year, and walked at two years. She had not gained control of the bladder at two and one-half years.

The feeding had been normal. With the exception of an occasional cold, no infections had occurred.

The father, forty-nine years of age, and the mother, thirty-five years of age, were well. Three children, a girl eight years old, one six years old, and a boy five years old, were normal. The twin sister was normal and at the age of four years had a normal blood picture.

Physical Findings.—At the time of admission (two and one-half years of age), the patient was definitely undersized. The head, chest, and abdominal circum-

Fig. 7.—Case 8. Normal and abnormal twin sisters.

ferences were 45, 48.5, and 50 cm., respectively. The length was 80 cm., and the weight, 8.5 kg. The temperature, pulse, and respiratory rates were 38° C., 138, and 22, respectively. The patient was pale. The abdomen was distended, and the liver and spleen were enlarged. The heart was slightly enlarged, and a soft, systolic murmur was audible. The fact was suggestive of the mongoloid type (Fig. 7).

Course.—From the age of nineteen months until the present time (four years), careful observations of the blood were made, particularly in relationship to experi-

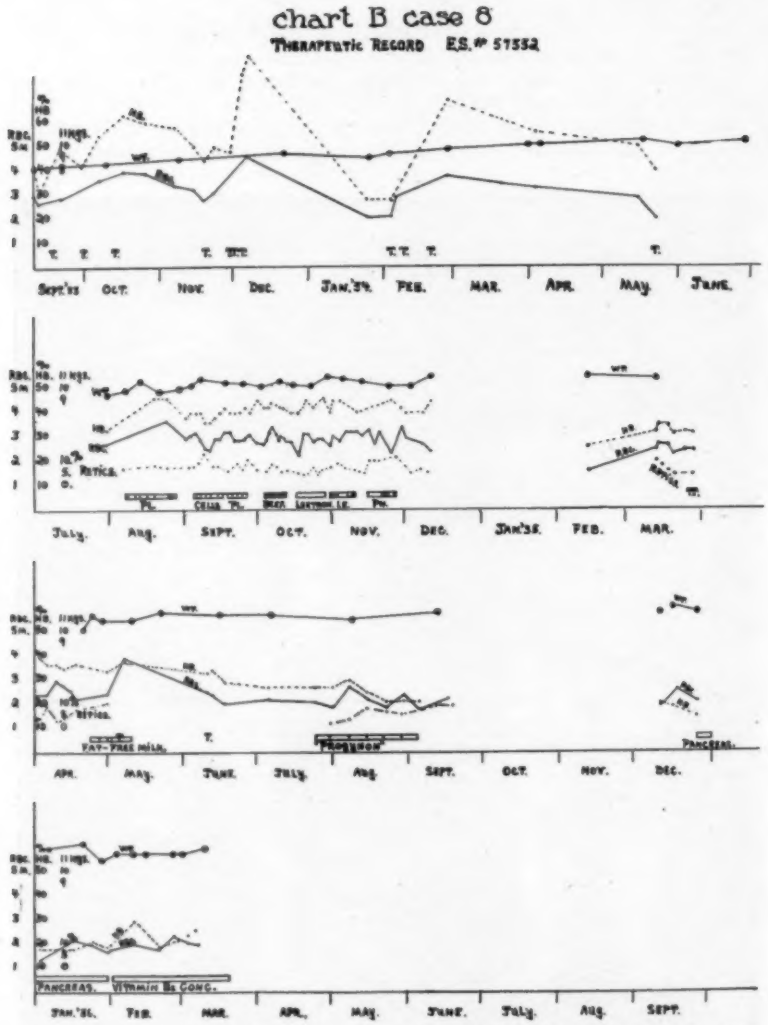
chart B case 8
THERAPEUTIC RECORD E.S. # 57332
Sept.'33 Oct. Nov. Dec. Jan.'34 Feb. Mar. Apr. May. June.
July. Aug. Sept. Oct. Nov. Dec. Jan.'35. Feb. Mar.
Apr. May. June. July. Aug. Sept. Oct. Nov. Dec.
Jan.'36. Feb. Mar. Apr. May. June. July. Aug. Sept.

Chart B.—Case 8. Explanation of dosages. *T*, transfusions of citrated blood given intravenously, 50 to 150 c.c.; *PL*, alcohol extract of blood plasma, 5 to 10 c.c. intramuscularly, 9 injections; *cells*, extract of blood cells, 5 c.c. intramuscularly, 7 injections; *PL*, alcohol extract of blood plasma, 5 c.c. intramuscularly, 5 injections; *beef*, 50 gm. of beef muscle incubated with normal human gastric juice, prepared by the method of Castle; *lextron* (Lilly), one teaspoonful t.i.d.; *LE*, liver extract (Lederle), 1 c.c.=33 gm. of liver substance, 8 injections; *PN*, pentnucleotide, 2.5 c.c. intramuscularly, 7 injections; *fat-free milk*, 5 intramuscular injections of 0.5, 1.0, 2.0, 3.0, and 4.0 c.c., respectively; *progynon*, intramuscularly, 7 weekly injections of estrogenic preparation (progynon-B, Schering Corporation), 1 c.c.=2,000 R.U. or 10,000 international units; *pancreas*, fresh, raw, beef pancreas ground, two teaspoonfuls every 2 hours daily; *vitamin B_1 concentrate* (Merck) 1 to 3 mg. daily.

mental therapy (Chart B). Among other studies made, the following may be informative: blood lipids: plasma—cholesterol, 125 mg. per 100 c.c.; total lipids, 594; phospholipids, 159; fatty acids, 469; residual fat, 300; red cell phospholipids, 366. These values are within normal limits.

Vitamin A absorption tests revealed the normal values as follows: fasting, 12 units vitamin A per 100 c.c. After 2 c.c. of haliver oil were administered, values were as follows: 2 hours, 35 units; 4 hours, 250 units; 6 hours, 286 units; 9 hours, 113 units; 12 hours, 119 units; 24 hours, 65 units. The b'ood calcium was 9.2 mg. per 100 c.c.; blood phosphorus, 4.4 mg. per 100 c.c.

Blood volume studies were made by Dr. Nolan L. Kaltreider, to whom we are indebted for the following information:

Body weight, 10.8 kg.
Red cell count, 2,300,000
Reticulated red cells, 6.0 per cent
Hematocrit-red cell percentage, 13.9 per cent
Hematocrit-plasma percentage, 86.1 per cent
Mean corpuscular volume, 60.5 cubic microns
Mean corpuscular hemoglobin, 16.6 micromicrograms
Mean corpuscular hemoglobin concentration, 29.4 per cent
Total plasma volume, 673 c.c.
Total plasma volume per kilogram, 62.3 c.c. (normal, 50 c.c.)
Total blood volume, 782 c.c.
Total blood volume per kilogram, 72.4 c.c. (normal, 72 c.c.)
Red blood cell volume, 109 c.c.
Red blood cell volume per kilogram, 10.1 c.c. (normal, 22 c.c.)
Hemoglobin per 100 c.c. blood, 3.82 gm.
Total circulatory hemoglobin, 29.87 gm.
Total circulatory hemoglobin per kilogram, 2.77 gm.
Blood viscosity, 2.3 (normal, 4-4.5)

DISCUSSION

Since the important work of Cooley, the clinical recognition of this type of anemia is no longer difficult. The blood picture is not entirely characteristic, however, because some of the features are duplicated in the blood of other conditions.

Observations on the morphology of the blood have confirmed the findings of Cooley[5] concerning the marked degree of fragmentation. Attempts to correlate hematocrit studies with cell measurements have been made.[3] In two cases a tendency to macrocytosis occurred particularly after splenectomy. A similar observation has recently been made in cases of hemolytic jaundice after this operation.[14] There was also evidence that in certain cases of *thalassemia* the red cell is thinner than normal.

Retarded growth, with a delay in carpal ossification, in certain cases, and sugar tolerance curves of the type obtained in Case 3 are features seen also in celiac disease. One does not find, however, the characteristic increase in the fat content of the stools in *thalassemia*. Moreover, in Case 8, the vitamin A absorption curve is normal as compared with the low curve usually found in celiac disease.

In our cases the blood lipids have been essentially normal. In Case 8 and in one other case not reported here, slight increases in the phos-

pholipid content of the red cells were found. Perhaps blood which contains many young cells is comparable with other growing tissues[18] known to have an increased phospholipid content.

In Cases 3 and 8, it will be noted that in each instance the total plasma volume and total blood volume per kilogram of body weight, as determined by the dye method, were normal. As might be expected, the red cell volume per kilogram of body weight was reduced, being only one-half normal in Case 8.

Because the pigment distribution in this disease resembles that in hemochromatosis, attempts were made to demonstrate urinary siderosis. Only an occasional iron-laden kidney epithelial cell was demonstrated in the urinary sediment.

Experimental Therapy.—Our attempts at experimental therapy have been mainly empirical. Our study of the anatomic material has led us to try substances which might supply material with which to build hemoglobin or cells. We have also tried certain glandular products. The hypoplasia of the adrenal cortex suggested the use of cortin. Although the results are entirely negative to date, we believe certain substances have been given sufficiently adequate trials to justify a report.

In Charts A and B, records of the experimental therapy used in Cases 3 and 8, respectively, are presented. The red cell count, hemoglobin values and the weight of the patient are shown by curves, beneath which is shown the time and duration that each therapeutic substance was used.

The therapeutic record in Case 3 (Chart A) is interesting because it covers his entire life from the time of diagnosis at seven months until death at five years. Of particular interest is the fact that repeated transfusions, splenectomy, the feeding of copper, of iron, and of various liver and spleen fractions have given negative results. Of the other substances tried, it seems certain that cortin (obtained through the courtesy of Dr. F. A. Hartmann, of Buffalo, N. Y.) and extralin were each given satisfactory trials. The oral administrations of such substances as anterior lobe, pituitary, thymus, and bone marrow extracts may represent inadequate tests. Extracts of these substances suitable for injection should, of course, be given a trial.

In Case 8 (E. S.) (Chart B) the parenteral injection of plasma and of cell extracts prepared according to the method of Josephs,[8] a potent liver extract preparation, and pentnucleotide have been adequately tested. The plasma and cell extracts were prepared for our use through the courtesy of Dr. S. W. Clausen. Except for a slight reticulocyte response to the cell extract and to pentnucleotide, no favorable results were obtained. Predigested beef prepared by the method of Castle[4] was also given an adequate trial in this patient without a response. Again this patient illustrates the temporary improvement expected from blood transfusion.

The *marrow* hyperplasia is a conspicuous feature of this disease, and in some respects it resembles the marrow of pernicious anemia. In both we have great hyperplasia of the marrow, which is unable to turn out adequate numbers of mature red cells but does flood the blood stream with immature and atypical red cells. One diseased marrow reacts to liver feeding but the other does not. However, one can scarcely avoid the thought[22] that the hyperplastic marrow in these children may be due to the *lack of something*—a deficiency state—as is surely true for pernicious anemia. These cases also may show nests of foam cells in marrow and spleen similar to the cells observed in Gaucher's disease. *Marrow metaplasia* with nests of myelocytes, nucleated red cells, and megakaryocytes may be noted in the spleen in most cases and in the liver and some lymph glands in some cases.

The changes noted in the *bony skeleton* are of some interest and by many writers are explained on the basis of marrow hyperplasia alone. We cannot agree with this belief and prefer to think of these peculiar lesions in the skull, ribs, and long bones as due to some metabolic factor. In other words, we prefer to think of these bone changes as of the order of those recorded in scurvy or acromegaly in which vitamins or ductless glands are concerned. Marrow hyperplasia in pernicious anemia or leucemia may be extreme and of long duration but does not give the bone abnormalities reported in this Mediterranean disease. Furthermore similar bone abnormalities have been noted in sickle-cell anemia and hemolytic jaundice, but the marrow changes in those diseases are of a different character.

The *pigment abnormalities* are conspicuous in this disease and follow accurately the pattern of pigment distribution in hemochromatosis. We[22] pointed out this similarity, but we cannot agree with Mallory[10] that this disease is "hemochromatosis in the child." This Mediterranean disease unlike hemochromatosis is racial, is associated with a progressive chronic anemia, splenomegaly, and characteristic bone abnormalities. We do not propose to join in the debate relative to copper as the cause of liver cirrhosis and hemochromatosis,[17] but we do feel that these cases of *thalassemia* give no support to this thesis and actually exclude copper as a cause of this particular pigmentary abnormality. If copper is the cause of the pigmentation of the viscera, then it is also the cause of the bone abnormalities and the peculiar anemia with splenomegaly, as these conditions always develop together in the same child. Also copper must injure especially the Mediterranean people and trail families like a bloodhound. It does not seem necessary to pursue the argument.

Pigments as they appear in tissues present difficulties of analysis, and this question has been reviewed recently by Nachtnebel.[11] Some pigments probably are of dietary origin, and many others come from hemoglobin. Others are thought to be related to fat metabolism (lipofuscin and lipochrome). One can at least differentiate the yellow granular

pigments into those giving a positive staining reaction for iron (hemosiderin) and those giving no iron reaction (hemofuscin, lipofuscin, lipochrome, etc.). Sheldon[17] concludes that hemofuscin is more nearly related to the melanins.

It is usually assumed that hemosiderin is related to blood destruction, but in hemochromatosis it seems difficult to accept this mechanism. Sprunt[20] was the first to point out that in hemochromatosis there was no increased blood destruction, and he suggested that hemochromatosis was due to a fundamental disturbance of the pigment metabolism. With this assumption we can record all the peculiarities of pigment deposit and abnormalities of hemochromatosis without forcing a relationship to hemoglobin destruction. The same thing may apply to the pigment abnormalities of *thalassemia*, although in this disease we do have a definite blood abnormality. The pattern of pigment distribution in hemochromatosis and *thalassemia* is almost identical; therefore the inevitable conclusion follows that the blood disturbance probably is not responsible for the pigment abnormalities in *thalassemia*.

The pigment deposits found in *hemolytic jaundice* are of interest in this connection. In long-continued cases we may find some pigment deposits in heart, pancreas, thyroid, and gastric mucosa, but the pigment deposits in spleen and liver are very different. In hemolytic jaundice the spleen shows great amounts of iron contained in the endothelial cells of the sinusoids, and the liver shows much of the iron-containing pigment in the Kupffer cells, an entirely different distribution from that recorded in *thalassemia*. The kidney, which shows little hemosiderin in *thalassemia*, is very heavily pigmented in hemolytic icterus. The experiments of Rous and Oliver[16] with long-continued injection of citrated blood in rabbits are of interest and present the same general picture as hemolytic icterus.

Pigment distribution in organs and cells is of some interest and, as relating to hemochromatosis, has been tabulated by Sheldon.[17] This pigment distribution is practically identical in *thalassemia*. One is struck with the observations that the gastric mucosa presents much hemosiderin which is present in the epithelium of the deep acini, particularly in the chief cells and rarely in the acid cells. Sharply at the pylorus the mucosa becomes hemosiderin-free, and pigment appears in Brunner's glands. The mucosa of the small and large intestine is free of hemosiderin except for occasional granules in phagocytes.

As we stated in our first paper, we dislike the name "erythroblastic anemia" given by Cooley, who was responsible for the recognition of the clinical syndrome. As the disease is limited to races of people living about the Mediterranean Sea, we suggested "thalassemia" as a preferable term derived from *Θάλασσα*, the Greek word for the "great sea"—designating in their writings the Mediterranean Sea.

SUMMARY

This disease is due to some racial, inherited defect which is responsible for the abnormalities of the hemopoietic tissues (of the order of pernicious anemia), the bone changes (of the order of acromegaly), and the pigment abnormalities (practically identical with hemochromatosis). This suggests a deficiency state which may be remediable when completely understood and gives adequate grounds for a variety of therapeutic tests.

We record in detail the complete autopsy findings in three new cases of this disease and partial autopsy findings in two others. We believe the pigment deposits in these cases (simulating hemochromatosis) are as characteristic of this disease as are the recorded abnormalities of the hemopoietic system and bony skeleton.

The anemia may be classified as microcytic and hypochromic. Macrocytosis and thinning of the cells occurred in two cases after splenectomy. In two cases (Cases 3 and 8) the total blood volume and the plasma volume were found to be normal, while the red cell volume was decreased. Wet preparations revealed marked fragmentation but no tendency to sickle.

The following therapeutic measures, which we believe have been adequately tested, failed to modify the clinical picture: blood transfusions, plasma and cell extracts, primary or secondary anemia liver extracts, fetal liver extract, spleen extract, raw pancreas, adrenal cortex extract (cortin), estrogenic substance (progynon), vitamin B_1 concentrate, iron, and copper.

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OBSERVATIONS ON THE MORPHOLOGY OF THE ERYTHROCYTES IN MEDITERRANEAN DISEASE—THALASSEMIA

(ERYTHROBLASTIC ANEMIA OF COOLEY)

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THE distinguishing features of the blood in Mediterranean anemia have been well described by Kato and Downey.[1] Marked irregularity in the size and shape of the red cells, fragmentation, and the comparatively large number of nucleated red cells in the circulating blood, particularly after splenectomy, are the essential findings. Irregularity in the distribution of hemoglobin within the matured erythrocyte is also found.

Hematocrit studies have indicated that the anemia in this disease may be classified as microcytic-hypochromic in type. Because of the extreme degree of fragmentation often encountered, Cooley[2] has suggested that incorrect results may be obtained by hematocrit studies. For this reason we have extended our observations to include comparison of the values obtained by the hematocrit with those found by direct measurement of the cells.

Hematocrit values and cell diameter curves have been determined in eight cases observed in the pediatric department of the Strong Memorial Hospital and in the out-patient department. All of the children were of Italian descent.

METHOD

Five cubic centimeters of venous blood were placed in bottles containing exactly 5 mg. of potassium oxalate, and from these samples red cell counts and hemoglobin determinations were made with certified equipment. The hematocrit readings were determined in Wintrobe tubes after centrifugalization for thirty minutes at 4,000 revolutions per minute.

The frequency of distribution of the cell diameters was determined by the method of Price-Jones.[3] A description of the ocular micrometer used was previously given by McCann and Dye.[4] All of the cell measurements were made by one individual (J. D.). To test our method further, a smear was examined by Dr. Price-Jones and the distribution curve kindly submitted by him was found to be practically identical with the duplicate made by one of us (J. D.).

The volume index was calculated according to the method of Capps[5]: the number of cubic centimeters of packed cells in percentage of normal divided by the number of red cells in percentage of the normal.

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The saturation index was determined by dividing the number of grams of hemoglobin per 100 c.c. of blood in percentage of normal by the number of cubic centimeters of packed cells per 100 c.c. of blood.

The thickness of the red cell was estimated by use of the three-dimension chart of Von Boros,[6] for calculating the thickness of the erythrocyte from the diameter and the volume.

The diameter-thickness ratio which best expresses the absolute thickness of the cell was calculated by dividing the mean diameter by the thickness.

The volume thickness index was determined according to the method of Haden.[7] For this purpose the nomogram described by Warburg[8] was used.

DISCUSSION OF RESULTS

Wet preparations revealed a marked degree of fragmentation. Knob-like projections were observed to form and to break off from the erythrocytes with regularity. One obtained the impression that many of these calls were leaflike and that they were thinner than normal erythrocytes.

Because Mediterranean anemia as well as sickle-cell anemia is racial and familial, and is characterized by similar bone changes, and since the sickle-cell type has been described in a Greek[9] as well as in an Italian[10] child, it seemed important to observe the blood carefully for the sickling phenomenon. This was studied in fresh and in carbon-dioxide treated blood at varying degrees of temperature, but no evidence of sickling was noted.

The results of the hematocrit observations are shown in Table I.* From these measurements it is apparent that the mean corpuscular volume is either normal or reduced. The combination of a decreased mean corpuscular volume and an increased mean-cell diameter (in the case of J. S.) suggests a cell thinner than normal. This is further shown to be true by the calculated cell thickness and the diminished volume thickness index.

If, as Haden[11] has shown, the volume thickness index is directly related to the fragility of the cells, we would not expect an hemolytic tendency to exist with a diminished volume thickness index. In the case of J. S., the resistance of the red cells to hypotonic salt solutions was found to be normal.

The same condition of an apparent thinning of the cells occurred in the case of T. Z. It is interesting that in these two cases (J. S. and T. Z.) the macrocytosis became evident after splenectomy had been performed. Paxton[12] has recently reported the occurrence of increased cell diameter in cases of familial acholuric jaundice after removal of the spleen.

*In the preceding paper J. S., aged eighteen months, is Case 3; J. S., aged seven years, is Case 5; while E. S., aged nineteen months, is Case 8.

TABLE I

MEASUREMENTS OF THE ERYTHROCYTES IN MEDITERRANEAN ANEMIA

PATIENT	AGE	DATE	RED CELLS (MILLIONS)	HEMOGLOBIN (GM. PER 100 C.C.)	HEMATOCRIT (C.C. OF CELLS PER 100)	VOLUME INDEX	SATURATION INDEX	MEAN CORPUSCULAR VOLUME (CUBIC MICRONS)	MEAN CORPUSCULAR HEMOGLOBIN (MICROMICROGRAMS)	MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION (PER CENT)	CELL MEASUREMENTS: MEAN DIAMETER (MICRONS)	STANDARD DEVIATION (MICRONS)	COEFFICIENT OF VARIATION (PER CENT)	CELL THICKNESS (MICRONS)	DIAMETER THICKNESS RATIO	VOLUME THICKNESS INDEX	INTERVAL SINCE LAST TRANSFUSION	DESIGNATION OF DISTRIBUTION CURVE (ON CHART 1)
Normal			*4.50*	*13.0*	*39.5*	*1.0*	*1.0*	*88*	*30*	*33*	*7.349*	*0.483*	*6.723*	*2.1*	*3.5:1*	*1.0*		
J. S.	18 mo.	5/31/30									5.849	1.169	19.9				68 days	A. J. S. ♂ 18 mo.
		6/11/30									6.610	1.084	16.4				2 days	B. J. S. ♂ 18 mo.
		12/ 5/32	3.30	6.5	25.0	0.86	0.79	75	19.6	26.1							29 mo.	Splenectomy 7/9/30
		5/23/33	3.70	5.4	25.0	0.77	0.65	67.5	14.7	21.6	8.073	1.789	22.0	1.35	5.9:1	0.66	34 mo.	C.
		6/20/33	3.23	6.6	25.0	0.87	0.81	78.1	20.6	26.4	8.330	2.182	26.2	1.45	5.7:1	0.71	35 mo.	
		8/15/33	3.28	7.2	22.5	0.78	0.96	68.6	21.9	32.0	8.421	2.046	24.2	1.25	6.7:1	0.60	37 mo.	
		10/ 3/33	1.88	3.5	14.3	0.88	0.75	76.0	18.6	24.4	7.647	1.900	24.9	1.70	4.5:1	0.90	39 mo.	D.
T. Z.	3½ yr.	6/26/33	2.60	5.0	18.7	0.81	0.81	72.0	19.2	26.7	6.268	1.010	16.1	2.30	3.1:1	1.50	13 days	A. T. Z. ♀ 3 yr.
		8/10/33	3.68	9.8	34.3	1.01	0.86	93.2	26.6	28.5	7.766	0.916	12.2	2.00	3.8:1	1.02	17 days	B. Splenectomy 7/24/33
		2/11/34	2.70	6.1	25.0	1.05	0.74	92.8	22.7	24.6	7.573	1.354	17.8	2.08	3.6:1	1.09	79 days	C.
		6/20/34	1.77	4.0	17.4	1.12	0.70	98.0	22.8	22.9	8.473	1.818	21.4	1.80	4.7:1	0.86	87 days	D.

TABLE I—CONT'D

PATIENT	AGE	DATE	RED CELLS (MILLIONS)	HEMOGLOBIN (GM. PER 100 C.C.)	HEMATOCRIT (C.C. OF CELLS PER 100)	VOLUME INDEX	SATURATION INDEX	MEAN CORPUSCULAR VOLUME (CUBIC MICRONS)	MEAN CORPUSCULAR HEMOGLOBIN (MICRO-MICROGRAMS)	MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION (PER CENT)	CELL MEASUREMENTS: MEAN DIAMETER (MICRONS)	STANDARD DEVIATION (MICRONS)	COEFFICIENT OF VARIATION (PER CENT)	CELL THICKNESS (MICRONS)	DIAMETER THICKNESS RATIO	VOLUME THICKNESS INDEX	INTERVAL SINCE LAST TRANSFUSION	DESIGNATION OF DISTRIBUTION CURVE (ON CHART 1)
E. S.	19 mo.	9/11/33	2.56	4.3	17.0	0.75	0.73	66.0	16.8	25.3							none	
		9/12/33	2.90	5.2	19.6	0.76	0.82	67.4	17.9	26.5	6.517	1.315	20.1	2.05	3.1:1	1.27	none	A. E. S. ♀ 19 mo.
		2/ 2/34	1.90	4.5	16.5	1.00	0.81	66.0	28.0	27.3	6.722	1.092	16.2	1.90	3.5:1	1.12	62 days	B.
		5/22/34									6.809	1.186	17.7				171 days	C.
		7/30/34	2.74	4.5	19.6	0.80	0.72	71.5	16.4	23.0							69 days	
		11/20/34	3.28	6.5	20.9	0.72	0.94	63.7	19.8	31.1	6.206	1.106	18.0	2.15	2.8:1	1.35	182 days	D.
		4/ 3/36	2.61	4.2	14.5	0.64	0.87	55.5	16.1	29.0	6.469	1.183	18.2	1.73	3.8:1	0.93	10 mo.	
P. G.	2 yr.	2/ 4/31	2.96	5.0	17.8	0.69	0.86	60.1	17.8	28.2	6.111	1.237	20.2	2.07	3.0:1	1.36	none	P. G. ♂ 2 yr.
R. M.	2 yr.	6/20/32	3.10	5.8	19.0	0.69	0.93	60.0	19.0	30.5	6.212	1.337	21.5	2.00	3.1:1	1.31	100 days	R. M. ♀ 2 yr.
J. S.	7 yr.	2/ 2/34	3.15	7.4	25.0	0.90	0.90	79.0	23.5	29.6	6.806	0.965	11.2	2.20	3.0:1	1.13	6 days	J. S. ♂ 7 yr.
B. D.	18 mo.	8/10/33									6.649	0.572	8.6					B. D. ♂ 18 mo.
J. D.	5 yr.	8/10/33									7.437	1.398	18.8					J. D. ♂ 5 yr.

In the cases, E. S., P. G., R. M., and J. S., microcytic curves were found, and the volume thickness index was either normal or slightly increased. None of this group had undergone splenectomy. Further observations on the cell morphology in relationship to splenectomy in this condition would be of interest.

The distribution curves (Chart 1) in general reveal wide bases and increased coefficients of variation. A similar Price-Jones curve was described by Monerieff and Whitby[13] in a Greek child. This report is said to be the first of thalassemia from England.

It will be noted from observation of Table I that blood transfusions preceded some of the studies. That a recent transfusion would ma-

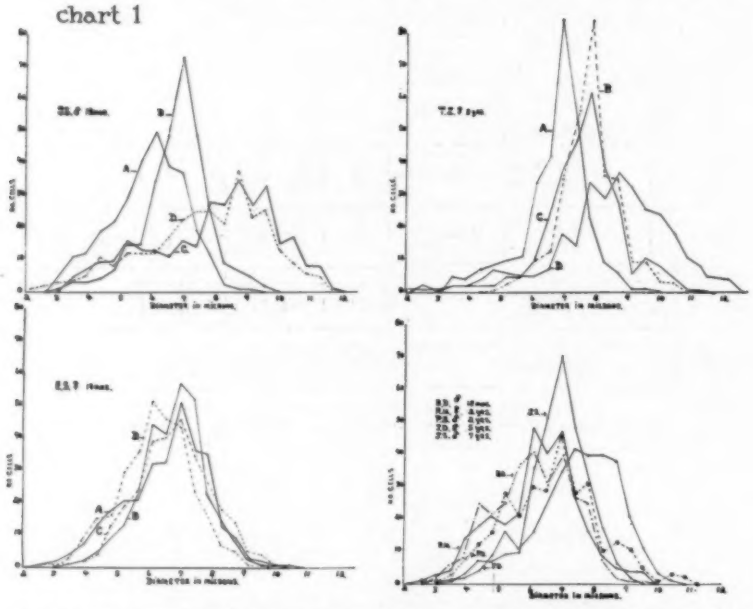

Chart 1.—Showing the frequency of the distribution of the cell diameters in eight cases of Mediterranean disease. In J. S. and T. Z. the tendency toward macrocytosis occurred after splenectomy.

terially change the results is admitted. How long such an influence would persist is not apparent because the life of transfused cells in this condition is not definitely known. Using the method of Ashby,[14] Edgar and Boisvert[15] have found from observations made in this clinic that transfused cells are no longer demonstrable after an interval of thirty to thirty-five days.

SUMMARY

Hematocrit studies in six cases and cell diameter measurements in eight cases of Mediterranean anemia (type of Cooley) have been made.

In all instances the evidence suggested an hypocythemic microcytic and hypochromic anemia.

In two cases the combination of decreased cell volume and increased mean cell diameter, along with decreased thickness of the cell, occurred after removal of the spleen.

Distribution curves usually showed wide bases and increased coefficients of variation.

The study of wet preparations confirmed the findings of Cooley and Lee that fragmentation of the erythrocytes is very marked. The phenomenon of sickling was not observed.

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INTRAVASCULAR CLOTTING IN ABANDONED FETAL CHANNELS IN THE NEWBORN

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INCREASED coagulation time, polycythemia, hemolysis, and bilirubinemia in the newborn are associated phenomena which present a problem of both a practical and theoretical significance. One of us has dealt previously with one aspect of this problem in a study of reticulocytes in the newborn (Krafka). In a search for the *raison d'être*, the investigation was extended to include the question of a correlation with the closing time of abandoned fetal vascular channels and the time of dropping of the cord. Gradually the hypothesis developed that these phenomena constituted in part or in whole a rational protective mechanism which prevented thrombus formation, since the thrombi, should they form, would serve as an embolic threat during this critical period of life.

Satisfactory tests of such an hypothesis are elusive, but we offer, as a preliminary approach, the following methods and results.

METHODS

Long umbilical cords were left intact on newborn infants. At specified times new double ligatures were placed near the end of the cord; the peripheral pieces were cut off and fixed immediately in 10 per cent neutral formalin or in alcohol. Successive pieces were removed at intervals of one and one-half hours, four hours, twelve hours, and forty-eight hours after birth. Cords dropping off normally on the fourth day were also fixed. Sections were cut in paraffin or celloidin and stained with hematoxylin and eosin, Mallory's triple stain, or Weigert's fibrin stain. By way of control, we have studied the clots in severed umbilical cords in which the general observation is made that clots will eventually form and in which the fibrin appears either fibrinous, granular or hyaline.

Nature of the So-called Clot in the Intact Vein.—One and one-half hours after delivery, a thin halo of pale eosinophilic, homogeneous substance occurs firmly adherent to the endothelium of the vein. This is approximately 20 mu wide. Well-preserved discrete erythrocytes and occasional leucocytes lie superficial to this zone with only a rare cell incorporated in it. No fibrin is present. There is no evidence of a reaction on the part of the endothelium.

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Such a clot, if it can be called a clot, has been described as a "hyaline clot." The nature of the homogeneous substance has been discussed by Welch, Aschoff, and MacCallum. They consider it to be made up of platelets in such close apposition that their borders are no longer visible. The hyaline clot has been interpreted as due to agglutination of erythrocytes, but in this instance, while the homogeneous substance is present, there is no evidence of a firm adherence of the red cells one to another.

There is no great addition to the width of this hyaline zone at the end of twelve or twenty-four hours. At forty-eight hours there is some evidence of hemolysis, but fibrin is still absent.

Even in the cord which has dropped, the so-called clot still shows the same characters, although the endothelium and media show marked degenerative changes. No fibrin is present. There is no organization of the clot such as produced by invasive connective tissue cells, connective tissue fibers or invading capillaries. Of course, organization would hardly be expected since it is thought to be initiated in the adult at about the tenth day. True clotting does not take place in the intact umbilical vein.

DISCUSSION

These observations are in accord with those of many investigators who have noted the absence of true clot in the abandoned fetal vascular channels. Meyer states that the intraabdominal portion of the umbilical vein contains unclotted blood in the sheep. He found red cells in a fair state of preservation in the dog at the end of the seventh week. Pöllot and other investigators have noted the absence of clot in the ductus arteriosus. Scammon in discussing the mechanism of closure of the ductus arteriosus states that less than 1 per cent show a clot at autopsy. Even in these instances, the nature of the clots is not established since they may be associated with infection at various other sites, as will be discussed below. Strassman (cited by Melka, 1926) believes that thrombosis of the ductus arteriosus is always pathologic. There are, however, some writers who still accept the theory of the closure of fetal channels by thrombus formation (Wiggers, Haberda). Meyer, Shaeffer, and Melka have dealt conclusively with this problem and have shown that the obliteration of the channels is brought about by contraction, infiltration of the intima, and obliteration of the lumen by connective tissue of the elastic type.

A casual review of the clinical literature is at first hand contradictory to the opinion that thrombosis of the fetal vessels does not occur. There are frequent references to cases of thrombosis of the aorta, sinus thrombosis, etc., in infancy. Careful study of these cases shows, however, that thrombosis is associated with infection at other sites, such as umbilical infection, fibrinous pneumonia, etc. Moscheowitz cites a case of death on the tenth day with thrombosis of the aorta following streptococcus

infection of the umbilical vein. Hedinger's patient died on the fifteenth day with gangrene of both feet and a putrid coagulum in the umbilical vein. Rothstein's patient died on the thirteenth day with thrombosis of the aorta, no gross external inflammatory changes but a staphylococcus infection in a thrombus in the umbilical vein. Limper and Miller cite a case in which the cord dropped normally on the seventh day; dry gangrene of the legs followed; and at autopsy the aorta was found occluded by a thrombus. The umbilicus showed infection. Wheler presents a case with black feet on the tenth day from a thrombus ¼ inch below the entrance of the mesenteric artery. Cultures showed pneumococcus.

We present two cases from the records of the Pathology Department of the University of Georgia School of Medicine:

Case 34,171.—Child died on the eighth day with infection of the right hand; suppurative infection of the umbilical stump; thrombophlebitis of the umbilical vein and septic infarcts.

Case 30,125.—Child died on the twelfth day with thrombosis of the pulmonary and renal veins, associated with rachischisis and a suppurative meningitis.

Even the so-called marasmatic clots are exceedingly rare in infancy and occur associated with infections. Blackfan lists three cases in infancy, the youngest child, twelve days old, with "associated with a scalp infection."

Thrombosis and embolism are not conditions of infancy. Cases due to infection, in which fibrin formation is excessive, are rare, an opinion supported by Byers and Hass from their study of sinus thrombosis.

We find one exception to generalization that thrombi do not form except when infection exists. Bettinger presents a case of a child dying on the tenth day with a thrombus of the ductus arteriosus (ductus Botalli). There were no clinical signs except cyanosis and spasm. Suspected cerebral hemorrhage associated with a precipitate delivery was not shown at autopsy. There was no apparent infection. Despite this one case, the conclusion seems to be justified that intravascular clotting in abandoned fetal channels does not occur, and we may next pass to a search for a rational explanation as to why it does not occur.

Many studies have shown an increased coagulation time in the infant. (Rodda, Lucas and associates). This period lasts approximately ten to fifteen days—well beyond the normal limits of the functional abandonment of the various fetal channels. Scammon and Norris have shown that in 2 per cent the ductus arteriosus is completely obliterated at from eight to fifteen days. In 18 per cent the ductus venosus is no longer patent at from eight to fifteen days. While complete obliteration in the remainder of cases may extend well into the first year, functional aban-

donment of the various channels is practically simultaneous with birth. Flow through these vessels then is practically nil, and flow is one of the four main factors postulated by Aschoff as necessary for the growth of thrombi by accretion of new platelets.

Hydrodynamics, however, are not the main factors involved since fibrinous coagulation fails to occur in the same way that it fails to occur between two ligatures placed on either artery or vein unless the ligatures are septic (Fourmestreux). Included erythrocytes remain discrete and intact or are hemolyzed and absorbed. There is no organization of clot as may occur in the adult. This is in keeping with the observed fact that extravasations into the brain, due to birth injuries, show no fibrin and are rarely organized. Levinson and Saphir have emphasized this point when they state that 9 per cent of all newborn show hemorrhage but very few show permanent defects resulting therefrom.

It will also be noted that increased coagulation time extends well beyond the normal limits for the time of the dropping of the cord. The latter event occurs generally on the fourth or fifth day and rarely as late as the fifteenth, unless infection exists. We believe that the conclusion is justified that increased coagulation time noted in infancy is not incidental but that it exists as a part of the mechanism which provides against thrombus formation during the period when the abandonment of fetal channels would constitute a serious embolic threat.

Many studies have been instituted in an attempt to associate increased coagulation time with the marked hemolysis and bilirubinemia noted in the first ten days of life. Mitchell reports an indirect van den Bergh in all children under fourteen days of age. Bonar claims that the icterus index reaches the birth level at the end of the twelfth day. Lucas and his coworkers claim that the bilirubinemia increases as the coagulation time increases. The degree of jaundice, however, has no essential part in the mechanism but is purely incidental. Ylppö has reviewed the various theories responsible for the cause of the bilirubinemia. It is generally considered normal although it may become pathologic.

Regarding the mechanism of clotting in the infant, Whipple has shown an increase in antithrombin. Lucas has pointed out the fact that the blood of the newborn shows no defect in retraction of clot in vitro and that no fibrinolysis occurs. The number of platelets are normal (Leslie and Sanford). Gelston reviewed the subject in 1921. Lucas thinks that the prolonged coagulation time is due to a platelet defect as in hemophilia. It is also generally held that bile pigments are marked anticoagulants, and hence the delayed clotting is due to the bilirubinemia since calcium is rendered inert by the bile pigments (Whipple).

Whether or not we accept this conclusion, the bilirubinemia of infancy appears to be not a part of a pathological process, but a part of

the normal mechanism (either cause or effect) which prevents thrombus formation during the critical period of vascular adjustment associated with birth.

The hypothesis here offered correlates a whole series of hitherto obscure and isolated events: (1) increased coagulation time; (2) bilirubinemia; (3) time of dropping of the cord; (4) time of abandonment of the fetal vascular channels; (5) absence of thrombi in such channels; and (6) absence of emboli except when infection exists. It affords a rational theoretical protective mechanism against the dangers of embolism during the period when the vascular bed is subject to the greatest amount of normal physiological insult.

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AN OUTLINE OF THE PEDIATRIST'S RELATION TO MENTAL HYGIENE

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IN SPITE of, or perhaps because of, the growing literature about mental hygiene in childhood, there is still considerable confusion as to the relative function of pediatrists and psychiatrists in this field. We quite agree with the viewpoint expressed last year before this Society by Dr. Crothers, that the "care of the whole child" is too large an order for any one man. In the present set-up the care of children must be participated in by physicians, nurses, psychiatrists, school-teachers, and all others whose businesses in life bring them in contact with children, the parents assuming the ultimate responsibility. We feel, however, that in his use of the term "whole child" he somewhat misinterpreted pediatric opinion in the matter, as we know of none who think that the entire responsibility for the welfare of children should rest in the physician's hands. Those who have stressed the importance of mental hygiene, education, and community life in the field of pediatrics have done so because they have felt that the children's specialist must look upon the child as a whole, not simply as a physical organism, and because they have been sensitive to the importance of environmental factors aside from disease as influences upon growth and development. It is a matter of fact that the "whole child" is influenced profoundly by the pediatrist, whether or not he intends to impress himself outside of the physical sphere.

In view of the rather loose discussions in recent years, it has seemed to us that a more explicit definition of the actual function of physicians in mental hygiene is needed. It is the purpose of this paper to present in outline form what may be considered proper fields of endeavor for the pediatrist.

We would immediately insist that in dealing with the problem as it exists today, the major effort of the pediatrist should be preventive. Physicans might be so well trained that they could treat serious psychiatric problems efficiently; but, since the rank and file are not so trained today, it would be an obvious error to advocate their assumption of this important service. The situation in the field of prevention, however, is entirely different. The pediatrist is the only physician who sees many children at a time in their lives when prophylaxis is applicable. Because of his unique opportunity and because preventive measures are

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not difficult technically, the children's specialist may reasonably be expected to undertake this most important task, during infancy and early childhood at least. Either he must accept this responsibility intelligently, or the whole matter will be relegated to chance.

In order to make their influence felt most forcefully, there should be unity in ideals and in technic so that physicians can present a more united front than is possible at present. Such unity can only be attained after careful consultation between representatives of the groups most interested, physicians, psychiatrists, and educators. The following outline is intended to list, merely, the subjects which seem most important to us.

I. Predominantly Physical Topics With Psychological Effects.

A. Habit formation. In some cases a transfer of subcortical reflexes to cortical control. The optimum age for training in each case must be considered.

1. Appetite.
2. Sleep.
3. Bowel and bladder control.
4. Physical skills.
5. Play.
6. Personal hygiene.

B. Associations with ill children. Bedside technic, pain, fear of doctor, suggestion, etc.

1. Treatment of disease.
2. Physically handicapped.
3. Fatigue.

C. Mental subnormalities on a physical basis. Possibilities for care at home and in schools.

1. Mongolism, cretinism, microcephaly, etc.
2. Brain injuries, hemorrhage, trauma, inflammation, etc.

D. Functional disturbances on a physical basis. Educational opportunities and our advice.

1. Reading and speech difficulties due to mixed cerebral dominance.

II. Predominantly Psychologic Topics With Physical Effects.

A. Emotions. Important in habit formation and personality development.

1. Fear.
2. Love.
3. Anger.
4. Hate.
5. Sorrow.

B. Conventionally unacceptable habits. The physician's opportunity in prevention and early treatment.

1. Lying.
2. Stealing.
3. Masturbation.
4. Thumbsucking.
5. Stammering.
6. Nail biting.
7. Tics.
8. Disturbed sleep.
9. Daydreaming.
10. Heterosexual activities.
11. Disorderliness and uncleanliness.
12. Temper tantrums.

C. Relation to society. From birth the physician must understand the complexity of the child's problem.

1. Negativism.
2. Pathologic attachment to mother and nurse.
3. Antisocial behavior.

D. Intellectual attainment. Physician must be able to give an approximate opinion.

1. Precocity.
2. Mental retardation.

E. Motor states. Physician must recognize types in order to fit individual into environment.

1. Hypermotility.
2. Hypomotility.

F. Adolescence. Understanding of major psychologic processes at this time.

III. Environmental Factors Modifying Development.

A. Education. Of major importance in physical and personality development.

1. Parent.
2. Nurse or nursemaid.
3. Physician.
4. Child's school.

B. Relation to other children in family. May be the cause of abnormal behavior in children.

C. Playmates.

D. Socio-economic factors. Perhaps the most important modern consideration in physical and mental health.

A discussion of all of these items would obviously require a text. However, in order to illustrate, we are selecting a few subjects for brief expansion.

It will require but few words before this Society to demonstrate that the child who has been so handled in relation to eating that he emerges from infancy with a pronounced aversion for food has suffered severe psychic trauma. Regardless of the cause of his anorexia or of the methods that have been used, such a child has been deprived of one of the basic pleasures of life. Good mental hygiene does not include such deprivation in its plan. But, serious as this aspect of the problem may be, it often becomes a minor consideration in the tense situations which too frequently arise. Children are still being browbeaten, threatened, and even literally forced and whipped into eating. Others are so pampered in efforts to secure ingestion of food that they become veritable tyrants in the family life. The bad psychic effects produced by these situations are too obvious to require elaboration. Any competent psychiatrist recognizes that such backgrounds are major causes of psychologic difficulties in older children and adults. It is the experience of the authors that anorexia is easily preventable except in rare instances of chronic physical disease; hence its prevalence is a direct challenge to us, an urgent demand that prophylactic measures be applied more widely.

Negativism is another type of abnormal mental reaction frequently encountered in developing children. In a sense it is the product of the child's awareness of his own individuality times the violence of external forces applied against it. Our attitude toward the child strongly influences these external forces. It is an easy matter for the pediatrist to recognize, even in early infancy, the type of baby who will be particularly resistant to coercion. The parents of such infants should be taught a tolerant attitude toward the growth and development of their babies so that they may learn to recognize in this exaggerated defense mechanism a trait which may be of extreme value to the individual later on and so that they may be reasonable in their early efforts at education. It should be explained to all parents that children face a tremendous task in developing from almost entirely egocentric animals at birth into quite reasonable members of society by two years of age. They should be shown that it is the function of adults to smooth the way rather than to make it more difficult by lack of respect for the child's individuality. It is our experience that the negativistic type of child is infinitely more worth while than his conforming neighbor, for the reason that he values himself more highly. In the prevalence of unhappiness in this type of patient, the pediatrist must recognize an appeal for preventive endeavor.

As an example of what we mean by the pediatrist's rôle in prevention, we may cite as an illustration mixed cerebral dominance. While this outline was being discussed between us, one of us was called to see

a five-year-old child with a cold. The cold was of no importance, but it was noted that the child was uncertain as to which hand to use in drawing. On going deeper into the matter, it was found the child could spell her name by picking letters from blocks but wrote her name forward or backward, the direction seeming to make little difference to her. Thus a serious fault was accidentally discovered and proper measures outlined as to her training and education—even to a change in the choice of schools which the parents had selected, on account of the methods used in teaching reading. Thus a purely "medical visit" for a condition of little and transitory importance led to the discovery of a serious condition and, we hope, to a plan which will in all probability avoid serious maladjustment in a few years. It was not our function to reeducate and retrain the child, but to plan a system of education and training which would avoid difficulties arising from mixed cerebral dominance. Experience has shown that when such a condition is unrecognized, early educational difficulties are almost sure to arise and that these frequently end in behavior problems which require the psychiatrist in their treatment.

All the items listed in the outline could be considered in a similar manner. The intelligence of our response to the call for prevention will be, in a measure, dependent upon our respect for and knowledge of the physical and mental growth and development of children.

THE PRESENCE OF THE MENINGOCOCCUS IN THE NASOPHARYNX OF NORMAL INDIVIDUALS, AND THE BACTERICIDAL PROPERTY OF BLOOD AGAINST THE MENINGOCOCCUS

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DURING epidemics of meningococcic meningitis many authors have reported high contact carrier rates. However, the presence of carriers has also been found during interepidemic periods. In 1931 Cameron[1] demonstrated four carriers in a group of twenty-nine persons swabbed, all of whom were in the same building. None of these individuals had been in contact with cases of meningitis. One of these individuals was still found to be a carrier one year later. In 1934 Rake[2] discovered carriers of the meningococcus in healthy individuals. Dudley and Brennan[3] in 1935 found a non-contact carrier rate as high as 60 per cent in a naval and military population.

As these observations are of practical importance to the pediatrician, during the past two years we have studied the carrier rate in a non-contact population. As it is also relevant to assess the importance of certain immune reactions in the blood of individuals who may be harboring strains of the meningococcus, we have investigated the bactericidal property of the blood of normal individuals and of noncontact carriers against various strains of meningococci.

TECHNIC

West tube swabs were taken of the posterior nasopharynx, planted, and spread on dextrose blood agar plates. The plates were incubated at 37° C. for twenty-four to forty-eight hours, and colonies were picked and examined microscopically. Cultures of these colonies were planted in carbohydrate media containing dextrose, maltose, and saccharose. A suspension of each culture was tested with polyvalent antimeningococcus serum. All strains isolated were found to be gram-negative diplococci and produced acid in dextrose and maltose but not in saccharose. They agglutinated with polyvalent antimeningococcus serum.

RESULTS

Previous to the present study we had isolated meningococci from 16 carriers in a group of 125 medical students. During the last two

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years of this study, 63 healthy adults mainly physicians and technicians were swabbed at approximately monthly intervals. In all, 1,227 swabs were taken over the two-year period. No less than 243 were positive for the meningococcus. The percentage of the total positive swabs taken was 19.8. The monthly percentage of positive individuals varied between 16 and 28, with an average of 20. For the two-year period, of the 63 healthy adults tested, no less than 26, or 41 per cent, showed the presence of the meningococcus in the nasopharynx at one time or another. In these 26 individuals, 11 were shown to be harboring the meningococcus fairly persistently. Thirteen carried the meningococcus intermittently, and in 2 instances cultures of the meningococcus were obtained on only one occasion. It was also noted that there was either a complete absence or a marked reduction in the colonies of meningococci when swabs were taken during an acute upper respiratory infection in any given individual. These findings are in general agreement with those reported by Rake.[2]

In 1934 Silverthorne and Fraser[4] demonstrated that samples of blood from many adults contained bactericidal power to a recently isolated strain of the meningococcus. Other adults and infants failed to manifest this property in their blood. These authors further showed that two infants with meningitis possessed relatively little or no bactericidal power in samples of their blood at the onset of the disease, but developed it after recovery. It was also shown that strains of meningococci vary in their ability to thrive in a sample of blood containing no bactericidal power when measured against a "virulent" spinal fluid strain. A "virulent" strain is one that is lethal to mice in the more diluted suspensions in the mouse-mucin test.[7] These findings furnish one with two facts, first, that strains of meningococci vary in their power to "invade" a nonbactericidal sample of human blood and, second, that individuals possess varying amounts of the bactericidal principle in their blood against virulent meningococci. In 1935 we[5] found that the bactericidal principle was present in serum or plasma and depended on the presence of complement for its action. We also demonstrated the specificity of the bactericidal power of blood against the meningococcus and were able to produce this property in the blood of guinea pigs by vaccination with recently isolated virulent cerebrospinal fluid strains. Recently, we[6] have explored and extended some of these observations. The relation of the bactericidal power of blood to the virulence of the microorganism has been studied. Using as a control test a previously known nonbactericidal sample of blood, and a virulent recently isolated cerebrospinal fluid strain of the meningococcus, we demonstrated that samples of blood from five carriers were bactericidal to this virulent strain and to each of the five carrier strains. One might suppose from these findings that carriers possess bactericidal property in their blood which has been developed due to the continued presence of the menin-

gococcus in their nasopharynx. Most of the samples of blood from carriers which were tested possessed this property to certain virulent spinal fluid strains. We also demonstrated that the power of meningococci to invade a nonbactericidal sample of blood was, in general, parallel to the virulence of strains as judged on the basis of the mouse-mucin test of Miller. By the use of the mouse-mucin test and the bactericidal test, eleven noncontact carrier strains were examined. Three of these proved to be as virulent as any of the recently isolated spinal fluid strains, and the remaining eight strains proved to be avirulent. In later studies, strains both from spinal fluid and noncontact carriers were found to be in a "midposition" in respect of virulence, and one spinal fluid strain was avirulent as judged by the results of these tests. This latter finding may be due to the lack of the rapid subculturing on suitable media of this strain before being received. Samples of blood obtained from two of the three carriers of virulent nasopharyngeal strains had marked bactericidal power to their respective strains; the third was not tested.

CONCLUSIONS

1. A total of 1,227 swabs were taken from 63 normal healthy adults over a two-year period; 19.8 per cent of these were positive for the meningococcus.

2. Sixty-three individuals were swabbed at approximately monthly intervals. On these monthly examinations the number of positive individuals varied from 16 to 28 per cent. No less than 41 per cent of the group of 63 were positive at one time or another during the two-year period. Eleven individuals were persistent, 13 intermittent, and 2 transient carriers.

3. Eleven noncontact carrier strains were examined by the bactericidal and mouse-mucin tests; 3 of these strains were found to be virulent, and 8 were found to be avirulent.

4. Carriers of the meningococcus possess bactericidal power in their blood to their respective strains whether these strains are virulent or avirulent. Also, samples of blood from carriers possess bactericidal power to certain virulent cerebrospinal fluid strains.

5. The determination of the virulence of strains of meningococci by means of the mouse-mucin and bactericidal tests may serve as a useful means of selecting strains for the preparation of therapeutic serum.

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MEDIASTINAL LYMPHOSARCOMAS IN CHILDHOOD

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INTRODUCTION

TO THE pediatrician malignant tumors of childhood bring to mind the Wilms' tumors of the kidney, the retinoblastomas of the eye, the neuroblastomas of the adrenals, and lymphosarcomas. The latter are usually associated with the intestinal and cervical tumors rather than the mediastinal group. However, the mediastinal lymphosarcomas are the commonest form of massive mediastinal enlargement in children (Cooke[1]) and perhaps the commonest form of lymphosarcoma. In six hundred fifty autopsies over a six-year period at the Children's Memorial Hospital there were only four cases of malignant tumors of lymphoid tissue. Two were mediastinal, and of the other two, one was situated in the cervical glands and the other in the lymphoid tissue of the ileum. In this paper we wish to present the clinical, roentgenologic, and pathologic findings in three cases of mediastinal lymphosarcoma. These cases appear to be of sufficient interest and rarity to be worth while reporting.

CASE I: CLINICAL AND LABORATORY NOTES

J. K. (Case 692-36), aged six years, was admitted to the Medical Service of the Children's Memorial Hospital on Jan. 8, 1936.

Complaints.—Lethargy and anorexia.

History.—The child had been seen one month previously by his physician when nothing remarkable was found in the physical examination of the chest. Two days before admission his physician was called to see him for the above complaints and found flatness over the entire chest, front and back, with displacement of the heart and trachea to the left. There was no respiratory distress. In the absence of fever, a tentative diagnosis of tuberculous pleurisy with effusion was made. The child was admitted to the hospital where the tuberculin test was found to be negative.

Several attempts at thoracentesis gave no results.

White blood cells numbered 8,050; polymorphonuclear leucocytes, 55 per cent; lymphocytes, 40 per cent; eosinophiles, 1 per cent; monocytes, 3 per cent; basophiles, 1 per cent. The urine was normal.

Roentgenologic Findings.—A chest film taken on admission revealed increased density throughout the right chest, associated with slight displacement of the heart and trachea to the left. Very little mediastinal enlargement was demonstrated (Fig. 1). A lateral view showed that the increased density was situated in the anterior part of the right chest, and that it was bounded posteriorly by a discrete convex

From the Children's Memorial Hospital.
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border (Fig. 2). There was also evidence of a small amount of free fluid in the right pleural cavity. Calcification was visible in the region of the right hilus, and a small calcified area, apparently a Ghon tubercle, was present, fairly well lateral in the lung, opposite the third interspace anteriorly. Fluoroscopic examination showed the displacement of the heart and trachea to be greater during expiration than during inspiration.

Fig. 1. Fig. 2.

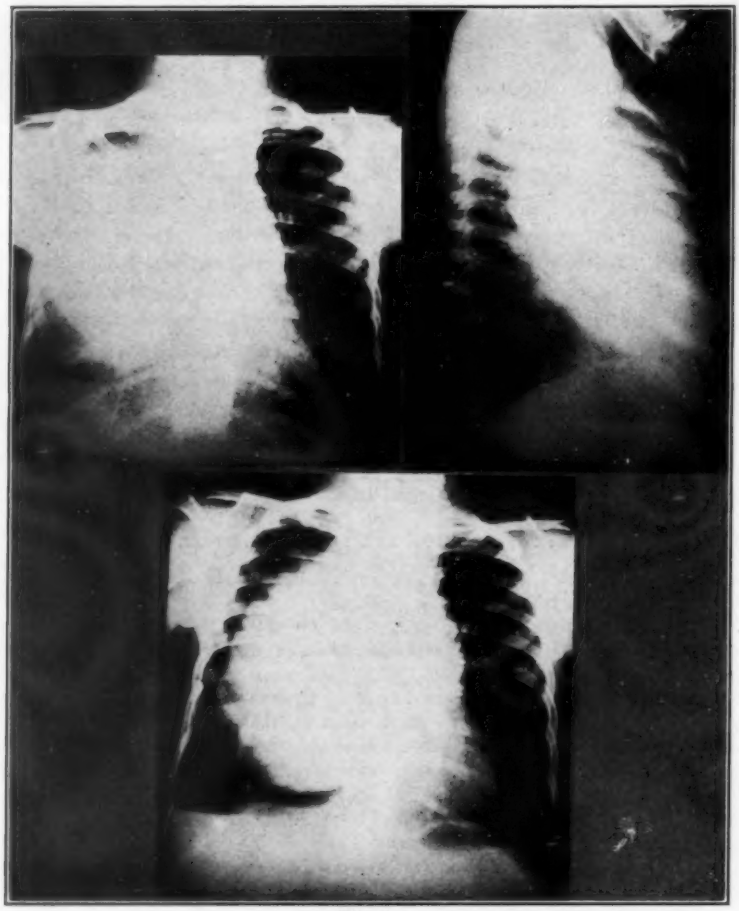

Fig. 3.

Fig. 1.—Case 1. Radiograph of chest on admission, showing right-sided increased density, and slight displacement of heart and trachea to left. The original film reveals calcification.

Fig. 2.—Case 1. Lateral view of chest on admission. The increased density is situated anteriorly.

Fig. 3.—Case 1. Appearance of chest following right-sided pneumothorax.

Reexamination of the chest one week later following the introduction of 80 c.c. of air into the right pleural cavity confirmed the presence of a small amount of free fluid on the right side. It also showed a large dense mass occupying the

anterior portion of the right chest. This mass measured approximately 8 by 13 cm. in diameter and its margins were quite discrete (Fig. 3).

The roentgenologic findings suggested a diagnosis of mediastinal tumor. Dr. F. A. C. Scrimger, surgeon-in-chief to the hospital, who saw the child in consultation, advised its removal. Operation was performed Jan. 17, 1936, under avertin and gas. The following is the operation report:

"One came upon a large, solid, tumor mass. It was up against the chest wall. The tumor was densely adherent to the lung, the whole of which was collapsed due to pressure of the tumor and was displaced laterally and posteriorly. The tumor itself was about the size of two fists and was encapsulated, the capsule being adherent to the chest wall and to the lung itself. A pedicle was felt which ran to the mediastinum. This was freed, thus liberating the tumor which was delivered into the wound. The pedicle of the tumor was then cut and removed. The tumor itself, on cutting into it, consisted of semisolid material and resembled grossly a sarcoma. Following removal of the tumor, the patient's condition appeared very poor, respiration stopping and the pulse growing very feeble. The lungs, however, were expanded artificially by means of a bag and intratracheal tube, and respiration was resumed after about five minutes. The child's condition then became poor, and, although artificial respiration was resorted to, he died before leaving the operating table."

Pathologic Findings.—Gross: The specimen, which was removed surgically, consisted of a large, somewhat pyramid-shaped mass weighing 470 gm. It measured 14 cm. from base to apex, 14 cm. in diameter at the base and 7 cm. in diameter at the apex. The capsule consisted of a thin veil of tissue in which there were areas of marked thickening. The point of excision could be seen as a break in the capsule through which tumor substance protruded. The cut surface presented a uniform yellowish white encephaloid appearance. A few, small, scattered hemorrhages were present throughout the tumor, and centrally there were streaks of bright yellow. A few indefinite septums radiated centrally for a short distance from the periphery.

The autopsy (A-36-9) was performed four hours after death and was limited to the removal of the thoracic and abdominal organs through the surgical incision. For this reason the relationship of the various viscera could not be accurately ascertained.

At the cephalic end of the mediastinum a stub of tumor tissue was found, to which the mass removed surgically had been attached. On the left side of the trachea in this region, there was a flat piece of tissue which grossly appeared to be the left lobe of the thymus. The paratracheal lymph nodes on both sides were enlarged to twice their normal size, were discrete and obviously infiltrated with neoplastic tissue. Both lungs were collapsed and congested. In the anterolateral portion of the upper lobe of the right lung, there was a subpleural, encapsulated, calcified nodule 0.3 cm. in diameter. Grossly this was a Ghon tubercle. In the hilus of the right lung there was a large caseous partially calcified lymph gland adherent to a neighboring bronchus. The remainder of the hilar glands on both sides was normal. No gross lesion could be seen in the left lung. Both pleural cavities were normal.

The anterior pericardium about the root of the aorta showed several large, thin, plaquelike masses extending down from the mediastinum. The pericardial sac contained a normal amount of fluid which, as far as could be made out, was not hemorrhagic. The tumor did not extend behind the pericardium.

The liver weighed 548 gm. as compared with the normal 642 gm. It showed no gross change. The spleen weighed 78 gm. (normal 58 gm.). The cut surface of the spleen was bright red and somewhat soft with the lymphoid nodules standing out prominently. The gastrointestinal tract showed no change except for a marked

prominence of the submucosal lymphoid tissue in the region of the ileocecal junction. The mesenteric and the retroperitoneal lymph glands, the myocardium, and the kidneys were normal.

Microscopic: Tissues were fixed in Zenker formol and formalin, embedded in paraffin and stained by differential methods. The sections from the surgical specimen showed most of the essential features of the tumor. They presented a strikingly uniform picture consisting of sheets of medium sized lymphocytic cells dotted at irregular intervals by larger pale staining cells (Fig. 4).

Some sections showed wide collagenous septums with finer strands branching off from these. They bore a distinct resemblance to the septums of the normal thymus gland. In one area, just beneath the capsule, were several small lobules separated by wide strands of connective tissue. These contained Hassall's corpuscles and were undoubtedly thymic tissue. The lobules were, however, completely replaced by tumor cells, which did not invade the surrounding connective tissue (Fig. 5).

Examination of a large series of sections showed the presence of a few normal and atrophic Hassall's corpuscles throughout the tumor. Many of these had almost completely disappeared, apparently as a result of invasion by the surrounding tumor

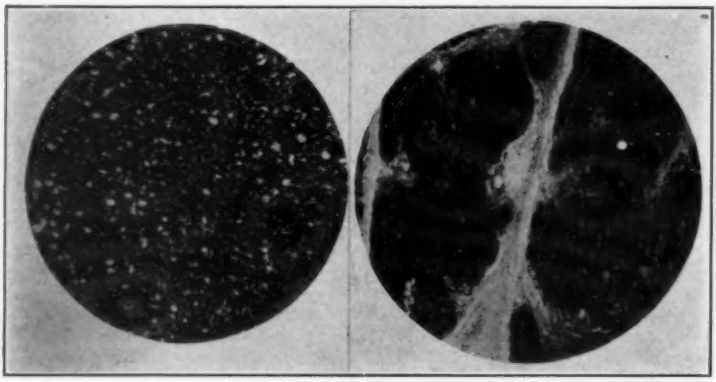

Fig. 4. Fig. 5.

Fig. 4.—Case 1. Low power photomicrograph showing tumor cells. Dotted at irregular intervals are pale staining reticular cells. Hemalum, erythrosin, and saffron stain.

Fig. 5.—Case 1. Low power photomicrograph showing thymic lobules at the periphery of the surgical specimen replaced by tumor cells which do not invade the trabeculae. Several pale staining Hassall's corpuscles can be seen surrounded by malignant cells. Hemalum, erythrosin, and saffron stain.

cells. The presence of fairly numerous eosinophilic leucocytes also served to identify this tissue as being originally thymus. The tumor cells themselves were of the medium-sized lymphocytic type. The nucleus was round, large, and more vesicular than the small lymphocyte, and contained a good deal of deeply staining chromatin, the amount of which varied somewhat from cell to cell (Fig. 6). The majority of the cells showed no visible cytoplasm, but a few had a narrow strip of nongranular, basophilic cytoplasm at one pole. There was, as a rule, one, but sometimes two, acidophilic nucleoli.

The most interesting feature of the sections was the presence of groups of closely packed cells which under low magnification gave the impression of staining more deeply than the remainder of the tumor cells. On oil-immersion examination, they appeared to have no cytoplasm, and their nuclei were actually larger and more vesicular than the type cell of the tumor. The depth of staining was due to

their being so tightly packed. Mitotic figures in these foci were very numerous as compared with the rest of the tumor (Fig. 7). There was a gradual transition in differentiation from the primitive cell areas into the surrounding more differentiated, more loosely packed tumor cells. These areas lay mostly beneath the capsule or in close contact with the collagenous septums. Like the germinal centers of the lymph nodes, they contained relatively few reticulum fibers as compared with the remainder of the tumor. As will be seen later, in the left lobe of the thymus, these primitive cell areas were the actively growing foci of the tumor.

The peculiar pale cells noted under low power magnification (Figs. 4 and 6) were round or branched, were wedged between the lymphocytes, and had nuclei which were mostly round or oval with scanty fine chromatin granules and one nucleolus, although many were pyknotic. The cytoplasm was acidophilic and contained numerous tiny vacuoles and a few basophilic granules. These cells, which were separated from each other by tumor cells, were numerous in some areas and scarce in others. They were present in both the primitive and differentiated cell areas. The vacuoles contained neutral fat droplets as shown by the scharlach R stain. These cells were obviously not fat cells, showed no evidence of activity, and

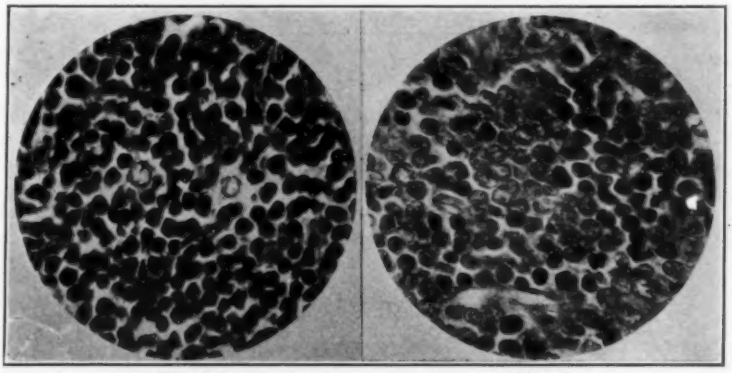

Fig. 6. Fig. 7.

Fig. 6.—Case 1. Oil immersion photomicrograph of tumor cells. Stain used does not demonstrate the vesicular appearance of the nuclei. Note the two reticular cells in the center of the picture. Compare this photograph with Fig. 7. Iron hematoxylin, Ponceau fuchsin, aniline blue stain.

Fig. 7.—Case 1. Same magnification and section as Fig. 6. This shows the cells of the primitive cell areas. Note the size, the vesicular character of the nuclei, and the numerous mitotic figures as compared with Fig. 6. Iron hematoxylin, Ponceau fuchsin, aniline blue stain.

did not appear to be taking any part in the tumor process. They were, in fact, the reticular cells of the thymus and appeared to be degenerating, as shown by the fatty droplets in the cytoplasm and the pyknotic nuclei.

In the sections of the tumor from the postmortem, the cell type was essentially the same as that in the surgical specimen referred to above. The mass on the left side of the trachea was in part thymus. Although it was extensively infiltrated by tumor cells, it had retained its lobulated structure, and the cortex and medulla could be distinctly made out. Besides a few Hassall's corpuscles in the medulla, these two were differentiated by the presence of numerous primitive cell areas in the cortex (Fig. 8), exactly similar to those seen in the surgical specimen. The medulla contained only the differentiated type of tumor cell. The same gradation between the two areas was present as was seen in the surgical specimen.

It would seem that the neoplastic process had originated in the cortex with subsequent involvement and replacement of the medulla by the lymphosarcomatous

process. The capsule of the left lobe was slightly infiltrated but was intact, except at one point where the tumor had broken through it and extended into the surrounding connective tissue.

Laidlaw's reticulum stain of the sections from the left lobe of the thymus showed a slight but definite increase in reticulum. This, in the normal thymic tissue, is very scanty and is mostly situated about blood vessels with almost none of the cortex. As in the normal gland, the reticulum was coarse both in the left lobe and in the main mass of the tumor in the right lobe.

The plaques noted grossly in connection with the parietal pericardium contained tumor cells. The inner surface of the pericardium was indicated by an irregular deposit of fibrin and red blood cells and an occasional cell of the serosal type. The opposite aspect of these plaques showed a thin collagenous layer, which was thymic capsule, for just within it was a zone of primitive tumor cells, similar to those previously described. The inner half of the plaque contained loosely arranged tumor cells and capillaries with a few strands of elastic tissue. These latter were probably remnants of the elastic tissue of the parietal pericardium. This section

Fig. 8.—Low power photomicrograph of capsule, cortex and medulla of the left lobe of the thymus. Note the densely staining primitive cell areas (for cell character, Fig. 7) in the cortex (top of photograph). Hemalum, erythrosin, and saffron stain.

clearly illustrates the reason for the early involvement of the parietal pericardium in thymic lymphosarcomas. It is a result of the involvement of that part of the thymus which normally overlaps the parietal pericardium about the root of the aorta. The frequent occurrence of hemorrhagic pericardial effusion in thymic tumors is explained by the extension of tumor cells from the overlying thymus into the parietal pericardium.

The hilar lymph nodes of the lungs were normal. Most of the lung tissue was atelectatic and congested. The pleura of the right lung showed focal microscopic involvement by tumor cells associated with hemorrhages. This invasion was probably due to direct contact with the overlying tumor. A few bronchi in both lungs were infiltrated with small lymphocytes and plasma cells indicating mild peribronchitis. Many groups of alveoli and even small lobules showed a mild lipoid pneumonia. The alveolar walls were thickened, infiltrated by small lymphocytes and had an epithelial-like lining. This lymphocytic infiltration appeared to be inflammatory rather than neoplastic, as the cells were small, stained deeply, and showed no mitotic figures or nucleoli. The alveoli were filled with vacuolated macrophages.

The caseous gland in the right hilar region was encapsulated and partially calcified. It showed no definite histologic evidence of tuberculosis beyond an occasional Langerhan type of giant cell. The calcified lesion in the upper lobe of the right lung was encapsulated by a dense fibrous tissue wall and was apparently a healed primary tuberculous focus.

The lymph nodes of the mediastinum were largely replaced by sarcomatous cells, but their architecture was distinct and a few primary and secondary nodules were present. There was a mass on the right side of the trachea which was probably thymus, as it showed a few indefinite Hassall's corpuscles, reticular cells and eosinophilic leucocytes. The neighboring connective tissues were extenively infiltrated by tumor cells, as contrasted to the tissues about the lymph nodes which showed relatively little involvement. The arterial walls were intact, whereas the venous walls had been invaded by the tumor cells. As will be seen later, this vascular invasion had occurred to a greater degree in the second case.

The mesenteric lymph nodes, the grossly hyperplastic lymphoid tissue of the cecum and ileum and their associated lymph glands showed no change that could be called neoplastic. The lymph glands about the upper abdominal aorta were normal with one exception. This latter was no larger than the others but was completely replaced by sarcoma cells. The capsule was not invaded, and there was no increase in the reticulum, but these fibers were widely separated by tumor cells. Except for this fact which seemed to favor metastatic invasion, it was impossible to say whether this isolated lymph node neoplasia was part of a systemic process or a purely metastatic involvement. The superficial lymph nodes due to autopsy restrictions could not be examined.

The liver, the kidneys, the adrenals, and the pancreas were free from tumor. The malpighian corpuscles of the spleen were clearly defined and contained well-developed germinal centers. The red pulp was markedly congested and contained cells of the lymphoid series with a few neutrophilic and eosinophilic polymorphonuclear cells. There was no suggestion of a leucemic process.

The bone marrow of the costochondral junction showed definite changes which gave rise to some controversy in their interpretation. Under low magnification, the marrow was seen to be unusually cellular due to the presence of numerous deeply staining cells either scattered diffusely through the marrow or arranged in small foci. The deeper staining cells consisted of a dense staining nucleus with a fair amount of basophilic cytoplasm about it. These were erythroblasts and were associated with a few polychromatophile erythroblasts and normoblasts. Most of this cell activity appeared to be erythroblastic.

Comparison with the costochondral junction of a six-year-old child who died of a congenital cerebral lesion showed a marked similarity between the two sections but there was greater cellular activity in the tumor case. Nevertheless, there were cells present which closely resembled lymphocytes in that they had almost no cytoplasm and fairly dense nuclei with nucleoli. These looked more like small lymphocytes than neoplastic cells. However, a few similar cells could be seen in sections from ribs of normal cases. The myeloid elements appeared to be normal. The slides from the costochondral junction were shown to a number of pathologists, of whom all but one believed it to be erythroblastic. One considered that the marrow might be sarcomatous. We believe it to be erythroblastic.

Diagnosis.—Primary lymphosarcoma of the thymus gland with involvement of the mediastinal lymph nodes, the parietal pericardium, right pleura, and one small retroperitoneal lymph node. Erythroblastic activity of bone marrow.

CASE II: CLINICAL AND LABORATORY FINDINGS

B. C. (Case 3096-35), aged eleven years, was admitted to the Medical Service of the Children's Memorial Hospital on March 6, 1935.

Complaints.—Malaise for two weeks following a respiratory infection. Easy fatigability, disturbed sleep, and nervousness.

Past History.—At one year she weighed 22 pounds. Following pneumonia at one year of age she developed celiac disease and was treated at various clinics. She had had measles and chickenpox. At the age of five years she weighed 25 pounds. She did not walk until five years of age.

Family History.—Her father died seven years ago of tuberculosis. A brother, aged thirteen years, has a positive Mantoux reaction.

Examination on Admission.—The examination on admission showed the child was surprisingly well developed and well nourished. She showed no signs of discomfort. There were signs of fluid in the left chest with displacement of the heart and trachea to the right. Temperature was 99.8° F.; pulse, 85; respirations, 22. Red blood cells numbered 4,420,000; white blood cells, 12,000; hemoglobin, 80 per cent; and the differential count was as follows: Polymorphonuclear leucocytes, 30 per cent; lymphocytes, 61 per cent; eosinophiles, 2 per cent; monocytes, 3 per cent; myelocytes, 4 per cent.

The Mantoux test was positive.

March 7: Left chest was aspirated, and 700 c.c. of reddish brown fluid was obtained. This fluid on smear showed differential counts of 90 per cent large lymphocytes with 10 per cent polymorphonuclears. Inoculated guinea pigs died of generalized tuberculosis. Between March 7 and April 2 she received four blood transfusions, which, however, did not control a progressive anemia; by April 10 the blood count was as follows: Red blood cells, 1,400,000; white blood cells, 23,000; hemoglobin, 30 per cent.

April 17: Red blood cells, 2,080,000; white blood cells, 18,400.

April 21: White blood cells, 19,800.

April 24: Red blood cells, 2,180,000; white blood cells, 88,050; platelets, 30,000; reticulocytes, 2.3 per cent, hemoglobin, 40 per cent.

The differential count of leucocytes was as follows: Neutrophile polymorphonuclears, 24 per cent; lymphocytes, 4 per cent; eosinophiles, 1 per cent; myelocytes, 2 per cent; metamyelocytes, 3 per cent; myeloblasts, 33 per cent; and unclassified, 33 per cent. (These were probably myeloblasts, but lacked the characteristic nucleolus.)

Goodpasture's stain showed 78 per cent of the white cells to be oxidase negative.

Later, in view of the autopsy findings, these cells cannot be interpreted as myeloblasts, but rather as primitive lymphocytes. The lack of gradation of these cells into adult cells of the granular series is in favor of this. The nuclei of these cells were vesicular as compared to the normal blood lymphocyte, and many contained nucleoli, thus resembling the tumor cells.

The spleen became at this time just palpable, while the axillary glands appeared to be slightly enlarged to palpation. A small nodular mass was felt at the left costal margin, which was thought to be enlarged abdominal glands.

On May 1 she developed generalized purpura and died on May 3.

Roentgenologic Findings.—A radiograph of the chest taken on March 7, 1935, revealed definite displacement of the heart and trachea to the right, and an extensive collection of fluid in the left pleural cavity. A bubble of air was present at the left apex, this film having been made following the aspiration of a small amount of pleural fluid, and resultant leakage of air. No lung detail could be seen on the left side, with the exception of a dense area which occupied the medial portion of the left apex above the fluid level (Fig. 9).

Examination on April 1, 1935, revealed slightly more marked displacement of the heart and trachea to the right, and showed that the left chest was completely dense. Examinations at frequent intervals showed gradually increasing cardiac displacement and showed that the left chest remained opaque.

The final examination on April 29, 1935, was made in the upright position, following the introduction of a small amount of air into the left pleural cavity. This air did not travel up higher than the fourth interspace anteriorly. The heart and trachea were tremendously displaced to the right (Fig. 10).

When this child was first admitted to the hospital, the presence of signs of fluid in the chest, together with a history of exposure to a tuberculous father and the finding of a strongly positive Mantoux reaction, naturally led to an initial diagnosis of tuberculous pleurisy with effusion. The first demonstration of bloody pleural fluid, however, made one pause and give serious consideration to a diagnosis of thoracic neoplasm.

Pathologic Findings.—Gross: The autopsy (A-35-42) was performed sixteen hours after death. There were numerous subcutaneous petechial hemorrhages over the abdomen and chest. The superficial lymph nodes were not enlarged. To the

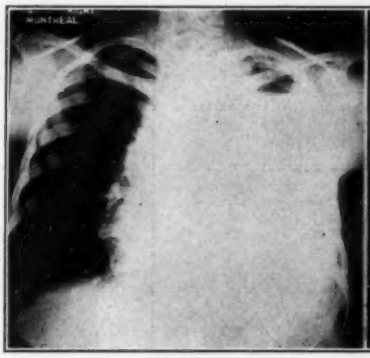

Fig. 9.

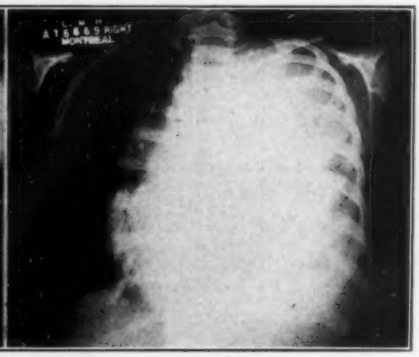

Fig. 10.

Fig. 9.—Case 2. Radiograph of chest following aspiration, showing left-sided fluid and air, a mass in the left upper medial chest, and cardiac displacement.

Fig. 10.—Case 2. Chest seven weeks after admission. The cardiac displacement has increased and air injected on the left side does not rise to the apex.

left of the sternum a diffuse nodular, slightly raised mass could be palpated just beneath the skin. On reflecting the skin of the chest, tumor tissue was encountered. This had reached the body surface by infiltration through the intercostal spaces to invade the muscles and the subcutaneous tissues. Upon opening the chest, the sternum in its upper half was adherent to a large hemorrhagic mass lying behind it.

This mass occupied the superior mediastinum, surrounded the trachea and the adjacent great vessels, had infiltrated and was adherent to the upper medial aspect and apex of the left lung (Fig. 11). Numerous large lymph nodes extended up from the apex of the tumor into the left anterior triangle of the neck. No trace of thymus could be found. The tumor involved the anterior surface and left lateral aspect of the parietal pericardium. A large hemorrhagic mass 3 cm. in thickness extended posteriorly to the pericardium as far down as the diaphragm. As a result of this, the heart was displaced to the right and ventrally. The trachea was displaced to the right of the vertebral column. The esophagus was similarly displaced to the right, but in its lower half it was also displaced anteriorly because of a chain of enlarged lymph glands lying behind it. These extended to the

diaphragm. The pericardial sac contained 250 c.c. of thin hemorrhagic fluid. There were smooth, large tumor masses bulging through a grossly intact parietal pericardium. The visceral pericardium and myocardium showed no gross involvement.

The right lung showed nothing of note. A small caseous lymph gland was found at the bifurcation of the trachea. Three-quarters of the left lung resembled a piece of beefsteak, and grossly suggested extensive involvement with tumor. The medial quarter of the lower lobe was atelectatic, but its appearance did not suggest tumor involvement. The left pleura was thickened, and the pleural cavity was filled with a layer of blood clot 3 cm. thick.

The lymph glands of the celiac axis were about four times their normal size, adherent to each other and sarcomatous in appearance. The left adrenal was involved by direct extension from these glands. The involvement of the celiac glands appeared to have taken place by direct extension through the diaphragm. The retroperitoneal and mesenteric lymph glands were grossly normal.

On cross-section, the mediastinal tumor presented a uniformly hemorrhagic appearance with large, white nodules, 3 cm. in diameter, situated posteriorly and

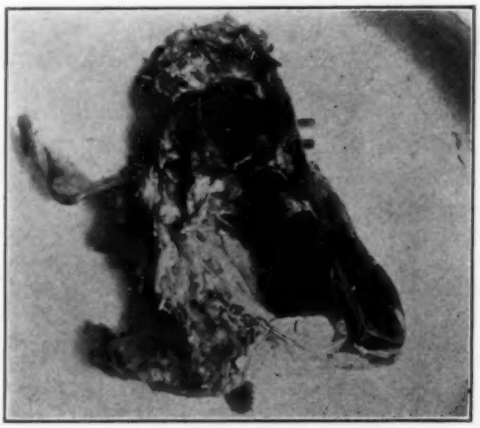

Fig. 11.—Case 2. Gross photograph of autopsy specimen. The mediastinal tumor is at the top of the photograph, part of the left lung can be seen to the right, while the posterior and left lateral aspect of the pericardial sac lies in the lower central portion of the photograph. The heart and anterior portion of the pericardial sac have been removed.

laterally. A few coarse trabeculae could be seen radiating into the tumor from the periphery. After removal of the pleura, masses of hemorrhagic tumor tissue could be seen plastered to the left side of the vertebral column and the posterior ends of the contiguous ribs.

The liver weighed 1,000 gm., as compared with the normal 909 gm. for this age. Its cut surface was yellowish and greasy, suggesting fatty infiltration. There was no evidence of tumor metastases. The spleen weighed 113 gm. as compared with the normal 87 gm. The cut surface was pale, and the pulp was firm to palpation. No nodules could be seen. The kidneys were grossly normal. The right adrenal was normal; the left adrenal was involved by direct extension from the glands of the celiac axis. The pelvic organs were normal.

The metaphysis of the right femur showed a firm white infarct measuring 1.4 cm. in length and 0.8 cm. in width. The metaphysis of the right tibia contained a more recent infarct in that it was soft and deep red in appearance. The surrounding

marrow was deeply congested but not unduly soft, and there did not seem to be any decrease in the bony trabeculae. The marrow in the center of the femur was normal.

Microscopic: Tissues were fixed in Zenker and bichromate formol, embedded in paraffin, and stained by differential methods.

The main mass of the tumor and the lymph gland metastases consisted of a fairly uniform cell type. These cells resembled those of the previous case and were of the medium size lymphocytic type (Fig. 12). Most of them appeared to consist wholly of nuclei, but a few had a thin rim of basophilic cytoplasm. The nuclei were vesicular, but less so than reticular cells, and showed some variation in chromatin content. The majority contained one or more nucleoli. They were closely but not densely packed and showed only a few mitotic figures. In addition to the main cell type, there were a few isolated cells which contained more cytoplasm and a vesicular nucleus and which resembled reticular cells. In the connective tissue bands running through the tumor and in the thickened pleura, a few small lymphocytes and neutrophilic and eosinophilic polymorphonuclear cells were present. Numerous sections from the region of the thymus were cut before any trace of thymic

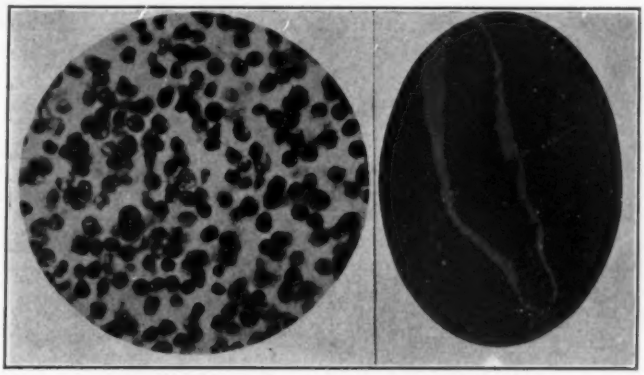

Fig. 12. Fig. 13.

Fig. 12.—Case 2. Oil immersion photomicrograph. The tumor cells are fairly uniform in size but show some variation in chromatin content. This is a more transparent stain than that used in Fig. 6, but the cells are similar. Hematoxylin, eosin azure A stain.

Fig. 13.—Case 2. Low power photomicrograph showing tumor cells in the lumen of a venous channel and attached directly to surrounding tumor by a pedicle passing through a break in the endothelial lining. Red blood cells are present in the lumen.

structure could be seen. In these areas small atrophic thymic corpuscles were present. Their scarcity and the fact that they were not found in the lymph gland metastases demonstrated that they were remnants of the thymus and not newly formed structures. Here, too, there was a rather indefinite suggestion of thymic lobulation.

The white nodules noticed grossly in the main tumor were incorporated lymph glands, with distinct capsules infiltrated by tumor cells. In these glands a few primary and secondary follicles could be seen. These findings would lead one to suppose that these glands were secondarily involved; otherwise it would be difficult to explain why the thymus should so completely lose its characteristic architecture while the lymph glands should maintain theirs. Diffuse hemorrhages were present throughout the tumor, particularly in the thymic region and throughout the connective tissues.

The walls of the arterial trunks were intact, while those of the venous trunks were extensively invaded up to and involving the endothelium. Throughout the whole mass, large venous channels were seen in which the infiltration of the wall had become so extensive that only the endothelial layer separated the tumor cells from the blood stream. In several instances these vascular channels actually contained masses of tumor cells and in a few these masses of tumor cells could actually be seen attached to the surrounding tumor by a pedicle of malignant cells extending through the venous wall (Fig. 13). This finding, and the fact that the lumina of blood vessels with intact walls contained cells closely resembling tumor cells, suggested the possibility of explaining at least in part, if not all, the terminal blood picture in this case. The parietal pericardium, like the veins, was extensively involved.

The left lung presented a most amazing picture which was difficult to interpret at first glance. It appeared to be infarcted in that the lung architecture had been wiped out, and the tissue appeared to have been wholly replaced by red blood cells, the arrangement of which occurred in groups separated by strands of fibrinlike material. With the aid of reticulum and elastic tissue stains, alveoli were indistinctly demonstrated in many places. On the other hand, numerous well-stained nucleated cells arranged either diffusely or in groups could be seen; the red cells were distinct in their outline, and very little fibrin was present. And thus we see that although it had characteristics of both a recent and a late infarct, it could not be classified as either, in that in the former case there would be no loss of lung architecture, while in the latter event there would be extensive necrosis and lack of cell outline.

Throughout the above mentioned lung tissue, groups of tumor cells were present; in some places the infiltration was extensive. In addition, there were numerous cells of different types, consisting of small lymphocytes, neutrophilic and eosinophilic leucocytes, with a scattering of myelocytes and a few plasma cells. The most interesting feature of the lung sections was the presence of giant cells with a large amount of basophilic cytoplasm. The nuclei were polymorphous; the majority were lobulated, stained deeply, and closely resembled megakaryocytes (Fig. 14). The adjoining atelectatic lung tissue contained numerous macrophages in the alveoli whose nuclei and general appearance resembled the above mentioned giant cells. It is possible that these megakaryocyte-like giant cells had risen from the histiocytes of the lung alveoli. There were no giant cells in the tumor. Benzidine stains showed the lung to contain relatively numerous peroxydase-positive cells as compared with the tumor proper, which contained none.

Sections in the region of the intercostal muscles, muscles of the chest wall, and subcutaneous tissues simply showed tumor infiltration between the muscle and collagenous bundles. The cells were of a uniform type.

The parenchymal liver cells showed patchy, fatty degeneration. Many, but not all, of the periportal spaces were infiltrated with cells. Yet the spaces were not enlarged, and there was no cellular invasion of the parenchyma. These cells consisted of small lymphocytes, a few eosinophilic polymorphonuclear cells, and the majority of cells resembled tumor cells. This involvement, although leucemic in type, was not as well developed as one would expect to find in a typical case of leucemia. The architecture of the spleen was not as well outlined as the normal. Malpighian corpuscles could be distinguished, but their boundaries faded indistinctly into the surrounding red pulp. The red pulp was unusually cellular and contained cells not unlike the tumor cells. Many of the cells were in the sinuses, while others appeared to be spreading peripherally from the malpighian corpuscles. Again, as in the liver, these lesions were not as well developed as in typical lymphatic leucemia. The kidneys were normal. The lymph tissue of the intestinal wall showed no deviation from the normal.

The lymph nodes in the region of the celiac axis were almost completely replaced by sarcoma cells, and there was extensive invasion of the surrounding tissues by these cells. The remainder of the retroperitoneal and mesenteric lymph nodes were normal in structure. Unfortunately no sections were made of the superficial lymph nodes. The caseous lymph gland in the mediastinum was histologically tuberculous.

The bone marrow of the sternum, costochondral junctions, ribs, and long bones showed similar neoplastic changes, and with the exception of the long bones, it was replaced completely by neoplastic tissue. The long bones showed extensive focal replacement, but the myeloid elements, while reduced in number, were still present. The megakaryocytes were few, and those that were present showed marked vacuolization. There was no diminution in number of the trabeculae of the bones. The infarcts which had been noted grossly were histologically true infarcts.

Diagnosis.—Primary lymphosarcoma of the thymus with direct metastases to pericardium, left lung, left pleura, left cervical lymph nodes, mediastinal lymph nodes, and the lymph nodes of the celiac axis, with leucemia-like involvement of liver, spleen, and bone marrow.

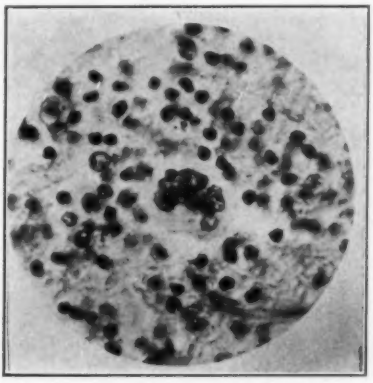

Fig. 14.—Case 2. Oil immersion photomicrograph showing a megakaryocyte-like cell in the infarcted left lung. Hemalum, erythrosin, and saffron stain.

CASE III: CLINICAL AND LABORATORY FINDINGS

T. L. (Case 2112-33), aged six years, was admitted to the Medical Service of the Children's Memorial Hospital on Feb. 9, 1933.

Complaint.—Swelling of the face, trunk, and legs.

Present Illness.—One month prior to admission the child began to lose her appetite, and at that time it was noticed that the eyes became swollen, particularly in the morning. The rest of the face gradually become involved. No other parts of the body were involved at that time, and the condition cleared up in about two weeks. The child returned to school, but two weeks later edema of the face again appeared and since then gradually spread to the trunk and legs. These symptoms closely resemble the so-called superior vena cava syndrome.

Physical Examination.—The child was well nourished. Weight on admission was 49 pounds. The submaxillary, left axillary, and left epitrochlear glands were all moderately enlarged. Otherwise there was no remarkable lymphadenopathy. The left side of the chest was more prominent than the right, but the expansion seemed equal on both sides. No tactile fremitus was present on the left. The percussion

note over the entire left chest was flat up to the first rib anteriorly and the second interspace posteriorly. The left border of the heart could not be made out. The right border of the heart was well to the right of the sternal edge. The right lung was resonant throughout. Tubular breathing was audible at the left apex, diminished breathing below. Breath sounds were present on the right side. There were no râles. The heart sounds were very distant, sufficient to suggest a pericardial effusion. There were signs of fluid in the abdomen. The liver was enlarged to the level of the umbilicus. The spleen was just palpable. The diagnosis lay between Pick's disease and a mediastinal tumor.

Laboratory Findings.—White blood cells numbered 17,200; platelets, 321,000; polymorphonuclear leucocytes, 51 per cent; lymphocytes, 38 per cent; monocytes, 6 per cent; eosinophiles, 2 per cent; metamyelocytes, 2 per cent; and basophiles, 1 per cent.

Blood urea nitrogen	17 mg.	Globulin	2.17%
Fibrinogen	0.73%	Total protein	7.56%
Albumin	4.66%		

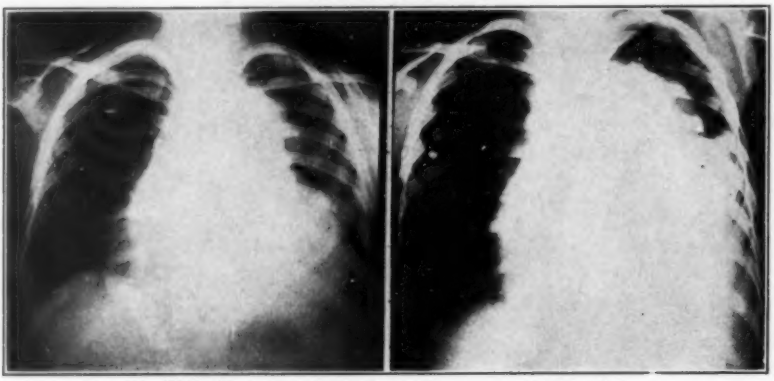

Fig. 15. Fig. 16.

Fig. 15.—Case 3. Film of chest made after aspiration of left-sided pleural fluid. The pericardium is enlarged to the right, and there is a large mass in the left upper medial chest.

Fig. 16.—Case 3. Chest nineteen days later. The pericardium is less markedly enlarged to the right, but the mass in the left upper chest has increased.

The Wassermann reaction was negative.

On aspiration of the chest 25 c.c. of straw-colored fluid was withdrawn. The total cell count was 9,500; specific gravity, 1.008 gm.; total protein, 20 per cent; chlorides, 305 mg.

Several further aspirations were done with rapid reaccumulation after withdrawal. Each successive thoracentesis yielded fluid which was increasingly sanguineous. Dyspnea gradually increased, and the child died April 2, 1933.

Diagnosis.—Lymphosarcoma of mediastinal origin.

Roentgenologic Findings.—The first film made on Feb. 9, 1933, revealed a rather extensive left-sided pleural exudate. A dense mass was present in the left upper medial chest, and the superior mediastinum was broadened to the right. The right border of the pericardial shadow was enlarged to the right, but its left border was obscured. A second film taken the same day following the aspiration of pleural fluid

(Fig. 15) showed the mass in the left upper chest considerably better, but otherwise added little information. The pericardium was still enlarged to the right, and the superior mediastinum was broadened to the right.

Examination during the month of February showed that the pleural fluid accumulated rapidly. A film was made on Feb. 28, 1933, following aspiration of fluid from the left pleural cavity and introduction of air, and also the withdrawal of 500 c.c. of pericardial fluid (Fig. 16). The mass in the left upper chest was seen to be larger and the right border of the pericardium was much closer to the midline. Aspiration of pericardial fluid produced similar changes on March 28, 1933, and by this time the left chest was completely opaque.

Pathologic Findings.—On March 2, 1933, biopsy of the left axillary glands was performed. Grossly and microscopically the glands were normal. Smears and paraffin sections of the pleural fluid were made on two occasions. These showed numerous red blood cells, polymorphonuclears, and discrete masses of atypical lymphocytes. The cells were of uniform size, larger than a small lymphocyte, stained less deeply, and consisted in most instances of an apparently naked nucleus with a nucleolus. Scattered through these were larger cells showing vacuolization, apparently degenerative. A few large cells with vesicular nuclei and basophilic cytoplasm were present. These cells, in view of their appearance and the fact that they formed discrete masses, were undoubtedly malignant lymphocytes.

DISCUSSION

Although the origin of the small lymphocyte-like cell of the thymus is still a moot point, for convenience we shall call them lymphocytes, while not committing ourselves to one or other theory.

It has been stated that in order to make a diagnosis of a primary thymic tumor, one must find typical thymic structures, especially Hassall's corpuscles. As the latter arise from the epithelial reticular cells and not from the lymphocytes, it does not seem logical that when the lymphocytes become neoplastic that they should give rise to Hassall's corpuscles. This appears to be supported by these two cases. In Case 1 the malignant process was obviously arising in the cortex of the thymus, as seen by the numerous areas of primitive cells from which the tumor spreads peripherally. There was an actual invasion of thymic medulla by cortical cells. In the right lobe where the process was more advanced, only a few thymic corpuscles could be found, while in the left lobe where the process was comparatively early, there was only an absolute reduction in the number of corpuscles. On close examination, tumor cells could be seen penetrating Hassall's corpuscles, separating, and peeling their layers off as one would peel an onion. As the process advanced, the corpuscles were destroyed. This also had happened in Case 2, in which only a few atrophic corpuscles could be found after cutting numerous sections. Then again, the direct metastatic infiltrations showed no attempt at formation of these bodies. If these corpuscles were being formed as a part of the tumor process, one would expect the reticular cells to be active, but there was no evidence to support this contention. Although the reticular cells were prominent in the first case, this was due to a degenerative

process; in the second case only a few of these cells could be seen. Thus it would seem that, whatever the origin of the lymphocytes, they, and they alone, composed the essential cellular structure of the newgrowth. They reproduced no other cells but themselves, and there was no histologic evidence to show that they were derived from the reticular cells of the tumor.

The first case speaks for itself in indicating that the mediastinal tumor was thymic in origin. There was a large tumor mass lying ventrad to the right lung with its stem attached to the mediastinum. This portion in its periphery showed undoubted thymic lobules, and throughout there were definite traces of thymic architecture and Hassall's corpuscles. This could not have been anything but the right lobe of the thymus. If the process had started in the mediastinal lymph nodes, it does not seem likely that metastases would have so outstripped the mother tumor in growth. Then, too, the lymph gland structure was well retained, and there was only slight infiltration of the tissues surrounding them, while, on the other hand, the tissues surrounding the thymus showed extensive involvement. The early pericardial involvement also points to a tumor of thymic origin.

The fact that the bone marrow may, and one extrathoracic lymph gland did, show early neoplastic changes, does not speak against a thymic tumor if one considers that the process may be a generalized one affecting other lymphoid tissue. That the thymic tumor could not be metastatic from these seems reasonable because the changes in other affected tissues were early—so early in the bone marrow as to make it doubtful that they were present. In addition, these areas did not show the primitive cell islands of the cortex of the thymus.

Ewing[2] states that thymic tumors are characterized by their position in that they surround and compress the trachea, bronchi, pericardium, and adjacent great vessels. The conditions are fulfilled in Cases 1 and 2 and probably in Case 3, as evidenced by the early development of edema of the face, although these conditions were complicated by the metastatic infiltration and the leucemia-like picture in Case 2.

In discussing Case 2, one meets with difficulties because it possessed the characteristics both of lymphosarcoma and leucemia, but, as has already been shown, the lesions have more of the properties of lymphosarcoma than of leucemia. It is becoming more and more apparent that there is no sharp dividing line between these two conditions and that there are undisputed instances which show features of both, but with one of them predominating. The term "leucosarcoma" seems justified for these cases, provided that it is used as a term to classify those cases which as yet, due to insufficient knowledge, cannot be placed definitely either in the group of the lymphosarcomas or the leucemias.

In our second case it seems to us that the thymus is the site of origin of the primary thoracic involvement. In this case Ewing's criteria were fulfilled. The lymph glands in the mediastinum were extensively involved but retained their architecture, while the thymus, except for a rare corpuscle of Hassall, had completely lost its identity. Here again, there was a greater amount of infiltration of the surrounding tissues in the region of the thymus than about the lymph glands. From the tumor in the thymus, the lesion was seen to invade the surrounding structures centrifugally.

Its neoplastic or lymphosarcomatous tendencies were well demonstrated by the infiltrative process which had passed through the thoracic wall to invade the muscles and subcutaneous tissues. The pericardium, the pleura, the left lung, and the lymph glands of the neck and celiac axis were also invaded by direct extension. However, we also found poorly developed lesions of a leucemia-like process in liver and spleen, but, contrary to expectations in a true leucemic process, the kidneys and many lymph glands were completely free of leucemic lesions. The bone marrow changes could be definitely classified as leucemic but were not as extensive as one would expect to find in true leucemia. This is in agreement with Heubner (quoted by Ewing) who says that with thymic tumors the other lesions of leucemia are not always well developed. Here, then, is a case in which were present both lesions of lymphosarçoma and leucemia but with a definite predominance of the characteristics of the former.

A review of the literature reveals that a remarkable feature of leucosarcomas is that the site of greatest involvement is in the mediastinum. Flashman and Leopold,[3] in a survey of the literature, reported that in a series of 107 cases the mediastinum was the probable site of the invasive tumor in 60. The next common site was the skin, the eyes, and eyelids in 22 cases. Ewing[2] states that the existence of a pure lymphocytoma of the thymus, apart from leucemia, does not appear to have been established. This is not in agreement with our first case; moreover cases in recent literature have been reported in which there has been a primary lymphosarcomatous tumor of the thymus without leucemia (Margolis[4]).

In connection with the leucemic changes often seen in association with tumor of the thymus, we would like to draw attention to several facts. In our cases the venous walls appeared unable to resist tumor invasion. This is most marked in the case in which tumor could actually be seen growing in venous channels (Case 2). These tumors were situated in a region where there are numerous and large veins. From these facts it is possible that a terminal leucemic blood picture may result from an outpouring of tumor cells directly into the blood stream. In Case 1 the venous involvement was not sufficiently exten-

sive to permit this to occur. Here, we would like to emphasize again the resemblance between the cells in the circulating blood and those of the tumor.

Whether the lesions apart from the main tumor are metastatic or part of a generalized systemic process affecting lymphoid tissue is a problem which cannot be satisfactorily explained. However, it is a fact that in primary tumors of the thymus distant leucemia-like involvement is common, but in lymphatic leucemia with generalized lymphadenopathy the converse has never been conclusively demonstrated. Margolis,[5] in a series of 32 cases of lymphatic leucemia, found tumor formation in the thymic region in only 4 cases, 3 of which were in children. In the remaining 28 cases, 7 of which were in children, there was no involvement of the thymus. He expressed the opinion that the 4 cases with thymic involvement represented a localized infiltration of the thymus by leucemic cells and that the thymus took no active part in the tumor formation. We are of the opinion that this was not conclusively demonstrated and that these four cases could equally well have been interpreted as being lymphosarcomas of the thymus. In fact, they appeared to resemble our second case. If the origin of the thymic cell is considered to be lymphoid, it is difficult to explain the absence of active involvement in lymphatic leucemia. On the other hand, if these cells are considered to have a different origin, the lesions apart from the main tumor could be interpreted as being metastatic in nature.

Interpretation of the clinical and roentgenologic findings in our cases is easy from the gross pathologic picture. The tumor mass in the superior mediastinum can give rise to symptoms and signs due to pressure on the veins, trachea, and nerves. Involvement of the pleura and the pericardium can be explained by infiltration. This gives rise to pleural and pericardial effusions which are often hemorrhagic. Our third case, from the clinical and roentgenologic standpoint, is identical with the second case, and the findings of typical tumor lymphoid cells in the pleural fluid established the diagnosis of mediastinal lymphosarcoma. In spite of its similarity to the second case, it did not have a leucemic blood picture.

The above signs and symptoms are late manifestations and are easily interpreted. It is unfortunate that the tumors must reach such a relatively large size before they produce symptoms which bring the patient to the physician.

SUMMARY

1. Three cases of mediastinal lymphosarcomas in children are reported. Clinically they were characterized by vague, early symptoms of lassitude, insomnia, and nervousness. Later, they gave rise to a fairly definite train of events, such as edema of the face, dyspnea, a

feeling of suffocation, and, above all, hemorrhagic pericardial and pleural effusions with displacement of heart and trachea. One had a terminal leucemic blood picture.

2. Roentgenologic findings were initially confusing in two of the cases, but in conjunction with the clinical and laboratory examinations, as well as the course, the malignant nature of the condition was soon established. Marked mediastinal enlargement was demonstrated in two cases, but the third case did not present this feature. Here the tumor was mainly situated in the right pleural cavity and simulated an encapsulated effusion.

3. The necropsy findings in two cases were such as to enable the diagnosis of primary lymphosarcoma of the thymus to be made. Both cases were characterized by large mediastinal tumors arising from the thymus, and, whatever the interpretation of the distant lesions may be, the thymic tumors themselves could not have been metastatic. In a large number of cases, a definite dividing line cannot be drawn between the lymphosarcomas and leucemias, and for these cases the term "leucosarcoma" is useful.

We wish to express our thanks to Dr. L. J. Rhea, for his constructive criticism of this paper, and to Dr. A. C. Kallan and Miss J. G. MacLeod, for assistance in preparing it.

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THE EVOLUTION OF THE ADULT TYPE OF TUBERCULOSIS FROM THE CHILDHOOD TYPE: EVIDENCE IN FAVOR OF ENDOGENOUS REINFECTION

A Preliminary Report

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TWENTY years ago, Baldwin[1] stated his feeling that "reinfection is mostly autogenous superinfection and due to disease, overstrain, trauma or any cause of lowered vitality, whatever that may mean." Since that time the feeling has grown steadily stronger that this source represents a smaller and smaller fraction of the so-called adult type of cases so that last year at the meeting of the National Tuberculosis Association this statement appears in Pope's communication:[2] "At the present time in this country the weight of scientific opinion leans toward the theory of exogenous reinfection as the determining factor in the etiology of phthisis, but it is doubtful whether the last word has been said upon this subject." Even if it be granted that for practical purposes the exogenous route represents the common source of reinfection, nevertheless completely to discredit the endogenous source, as is implied in Weintraub's report,[3] is going to an extreme not warranted by the facts. Following a group of approximately 500 reactors who were also contacts and 500 who were not, this author reports eleven cases deriving from the contact group and none from the noncontact. The children were followed for varying periods up to five years.

The observations reported here were made on 650 reactors who are wards of the Society of St. Vincent de Paul in Detroit and 150 contacts who were not reactors. On being assigned to this society from the probate court following the rupture of a family group because of disease, economic distress, or legal difficulties, the children are hospitalized and thoroughly checked before being placed in country boarding homes under foster parents. The homes are frequently inspected, and in those instances in which reinfection type disease occurred the foster parents were checked by x-ray when possible.

In seven years there have been detected in this group 23 cases of adult type of tuberculosis. Of these, 7 were discovered on first examination; 16 cases developed under observation. In only 2 of these was

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Conducted for the Society of St. Vincent de Paul at the Henry Ford Hospital in cooperation with the Children's Fund of Michigan.
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any question raised of reexposure, and in 1 of those 2 the adult lesion did not appear until ten months after the second exposure.

The ages at which the adult lesion appeared coincided with the usual experience; 5 cases appeared between three months and nine years; 15 between ten and seventeen years, and 3 between eighteen and twenty-two years.

One of the several objects of this study was to ascertain, if possible, whether or not we might affect either the incidence of, or the mortality from, the adult type lesion by a system of constant supervision which included preventorium care in a summer camp. Myers and his associates[4] recently stated their feeling that "at the close of fourteen years' observation we are unable to see any difference in the course of the disease regardless of whether the child so treated is a strict bed patient or remains as active as any normal child should be." At the same meeting Hawes[5] pointed to the record of the Prendergast Preventorium to uphold the opposing point of view. Out of 704 children followed, there had developed only 3 adult type of cases with 1 death, while in an identical number of reactors not supervised there had developed 40 cases with 10 deaths. We are unable to show anything like such a low incidence, but our mortality is equally gratifying.

A tabulation of the reports of various groups is interesting in this connection (Table I).

TABLE I

	REACTORS DEVELOPING REINFECTIONS	DEATHS
Pope	38	12
Myers et al.	36	8
McPhedran and Opie[6]	26	5
Hawes (Preventorium group)	3	1
Hawes (No preventorium)	40	10
Detroit group	16	2

This record of a group of children from the lowest economic and nutritional stratum would seem to us, even over so short a period as seven years, to justify the existence of the preventorium plan.

Table II lists reinfection types that have been discovered, together with the time elapsing between the finding of the first infection and the demonstration of the reinfection.

It was our hope to acquire some information on the question of the state of allergy at the time of the reinfection phenomenon, and with this in mind serial dilutions of tuberculin were applied on each examination of the child. The technic involved and the results obtained in another study limiting itself strictly to the first infection were described elsewhere.[7] In that study we found that, quantitatively con-

TABLE II

REINFECTION TYPES OF TUBERCULOSIS DISCOVERED IN SEVEN-YEAR STUDY

NO.	NAME	SEX	AGE REACTIVITY DISCOVERED	X-RAY EVIDENCE CHILDHOOD INFECTION	AGE AT REINFECTION (YR.)	TYPE
1.	J. K.	M	7	Yes	13	Pul.
2.	R. J.	F	13*	No	13	Miliary bone
3.	V. G.	F	14*	No	14	Pul.
4.	I. K.	F	9	Yes	17	Miliary†
5.	G. C.	M	2 mo.	No	3 mo.	Miliary†
6.	E. G.	F	11*	No	11	Pul.
7.	M. C.	F	16*	No	16	Pul. bone
8.	L. DeM.	F	15*	No	15	Pul.
9.	J. DeM.	M	16	No	17	Pul.
10.	D. B.	F	5	Yes	11	Pul.
11.	J. C.	F	4	Yes	6	Pul.
12.	C. K.	F	15	Yes	18	Pul.
13.	R. P.	F	5	Yes	9	Pul.
14.	J. C.	M	10	Yes	12	Pleurisy
15.	M. F.	F	19*	No	19	Pul.
16.	S. F.	M	16	No	17	Pul.
17.	J. F.	F	11	Yes	12	Pul.
18.	M. S.	F	2	Yes	9	Pul.
19.	A. M.	M	10*	Yes	10	Pul.
20.	G. G.	F	9	Yes	15	Pul.
21.	R. C.	F	7	Yes	11	Pul.
22.	G. R.	M	15	Yes	22	Pul.
23.	K. K.	F	7	Yes	14	Pul.

*Reinfection type when first seen.
†Deaths.

sidered, allergy followed a parabolic curve, the rise and fall seeming independent of the immune process, at least so far as that was measurable by the reaction in the peripheral blood, and we concluded that the evidence of that study favored the view that the two phenomena were independent. Observations on this group of children can be similarly interpreted. From Table II it will be seen that in terms of the heights that are commonly seen in first infections, allergy is not particularly high at the onset of the adult type lesion and that instances are found of its occurrence coincidentally with rising, falling, and level thresholds of allergy.

TABLE III

LEVEL OF ALLERGY AT THE ONSET OF THE ADULT TYPE OF LESION

MG. O. T.	NO. CASES	LEVEL IN ADULT TYPE CASES ON 1ST. EXAM.
0.1	7	
0.01	2	4
0.001	4	2
0.0001	2	
0.00001	1	1

Cases showing increase in allergic level on reinfection	7
Cases showing decrease in allergic level on reinfection	5
Cases showing no change in allergic level on reinfection	3

Finally, it was our hope by a study of the individuals showing the transition to learn something of the so-called "lowered vitality," of which Baldwin speaks as a factor influencing the development of the adult lesion.

A comparison of the weights of these children with expected weight yields little information as was pointed out long since in the Philadelphia study, but a study of the individual weight curves over a period of years has been very instructive. There is evident quite regularly a flattening of the curve in the year preceding the development of the lesion which is often the first abnormality to attract attention. With the thought that a study of the metabolism of these children might afford some evidence of subnormality in their nutrition at the onset of their lesion, serial basal metabolism determinations were done and the nitrogen balances were determined. The total metabolic rate in the adult with pulmonary tuberculosis and his nitrogen requirements have been reported by McCann,[8] who found them within normal limits and who reasoned that the elevation which might be expected as a result of infection was offset by the malnutrition that all of his subjects showed. He warned, however, that his conclusions should not be applied to the adolescent. In general, it can be said that our findings do suggest that an element of malnutrition dominates the picture, the total rates being approximately normal, but the basal metabolic mixtures and the retentions of nitrogen suggesting definitely that stores had been depleted. The metabolic mixtures in several instances show a steady rise in the amount of carbohydrate oxidized and the reciprocal fall in fat such as are seen in the recovery from fasting. It can be objected that these findings are impossible to interpret in terms of cause and effect, and that is true, though practically all were obtained before the disease process had advanced far. In any case they disclose elements of depletion often concealed by a deceptively normal weight. The details of this phase of the study will be presented in another communication.

SUMMARY

1. Six hundred and fifty reactors and 150 contacts who were not reactors, from a poor economic stratum, were observed for varying periods up to seven years following removal from their source of infection. There were found 23 adult type of cases, 16 of which developed subsequent to the initial observation.

2. There have been only two deaths, these from miliary tuberculosis, since the study started, a result which is interpreted as favoring the view that something has been accomplished by this system of follow-up and preventorium care.

3. No consistent relationship could be discovered between the onset of the reinfection type of tuberculosis and a quantitative change in allergy.

4. The basal metabolism of this group was found to be approximately normal. The metabolic mixtures and the retentions of nitrogen suggested depletion of metabolic stores.

The x-ray plates were interpreted for the first four years of the study by Dr. Henry D. Chadwick and the author and independently by Dr. H. Doub. In the last three years they have all been reviewed by Dr. Bruce Douglas and the author after an initial reading by Dr. Doub. In the metabolism studies we have had the assistance of Dr. F. W. Hartman, Dr. O. H. Gaebler, and Dr. J. W. Maroney. Dr. F. Janney Smith, of the cardiorespiratory clinic of the Ford Hospital, was in charge of the examinations of all of those patients over fifteen years old.

The tuberculin has been a single lot prepared by Dr. Leroy Gardner, at Saranac Lake.

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A STUDY OF THE COMPARATIVE VALUE OF COD LIVER OIL, VIOSTEROL, AND VITAMIN D MILKS IN THE PREVENTION OF RICKETS AND OF CERTAIN BASIC FACTORS INFLUENCING THEIR EFFICACY

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A SERIES of investigations with the purpose of studying the relative efficacy of cod liver oil, viosterol, and several forms of vitamin D milk given at different dosage levels were carried out in Detroit, Mich., during the winters of 1933-34, 1934-35, and 1935-36. The studies were planned with a view to developing practical methods of testing the value of the various antirachitic substances as administered by physicians and other public health officials to infants living in their own homes.

At the time the investigation was started in the fall of 1933 the belief was current that from 500 to 600 U.S.P. units of cod liver oil and two and one-half to three times as many units of viosterol were necessary to prevent rickets. The work of the first two winters was planned, therefore, to study this supposed relationship between the preventive dose of cod liver oil and of viosterol and to attempt to establish a base line for later comparative studies with vitamin D milks.

During the first winter cod liver oil was prescribed in doses of 540 and 270 units daily and viosterol in doses of 1,350 units daily, or two and one-half times the higher dose of cod liver oil. Due to the high potency of the viosterol (1,350 units in 3 drops) and to the tendency of the mothers to give more rather than less than the number of drops ordered, the amount of viosterol taken by the infants during this first winter was considerably larger than that intended—approximately 2,000 units daily.

The results of the first winter's work showed a complete absence of cases of moderate and marked rickets and a relatively small incidence of slight rickets among infants taking this large amount of viosterol, whereas a few cases of moderate rickets and a somewhat larger percentage of slight rickets occurred among the infants receiving cod liver oil.

From the Children's Bureau, United States Department of Labor, and the Food and Drug Administration, United States Department of Agriculture, with the cooperation and assistance of the Children's Hospital of Michigan, the Detroit Departments of Health and Welfare, the Children's Fund of Michigan, and a number of hospitals that permitted access to their records of newborn infants.

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During the second winter, therefore, the dosage level of viosterol was decreased and that of cod liver oil increased. Viosterol was prescribed at dosage levels of 1,350 and 675 units and cod liver oil at 675 and 810 units, with one level, therefore, in common. The dosage levels prescribed for cod liver oil and viosterol during the first two years are shown in Table I.

TABLE I

ANTIRACHITIC SUBSTANCES AND DOSAGE LEVELS IN U.S.P. UNITS PRESCRIBED DURING 1933-34 AND 1934-35

TYPE OF ANTIRACHITIC	AVERAGE NUMBER OF UNITS PRESCRIBED DURING	
	1933-34	1934-35
Cod liver oil	270	675
	540	810
Viosterol	1,350*	675
		1,350

*Dosage prescribed was 1,350 units daily; amount actually taken daily was approximately 2,000 units.

At the end of the second year the findings pointed to the fact that cod liver oil and viosterol administered at the level of 675 units were, to all intents and purposes, equally efficacious or at least that viosterol was no less effective than cod liver oil. It seemed apparent that the differences ascribed to the two forms of vitamin D did not exist in fact and it was believed that the minimum preventive dose (using the absence of moderate or marked rickets as the criterion) was probably in the neighborhood of 675 units. When judged by the presence or absence of slight degrees of rickets, the minimum dose may well be still higher since there is evidence that in the group receiving the higher dosages of viosterol the amount of slight rickets is less than in any other group. The presence of this slight degree of rickets, moreover, among a considerable proportion of infants receiving 675 units made it seem undesirable to repeat the studies of these antirachitic substances at lower dosage levels.

During the third winter attention was turned toward the study of milks. Four forms of evaporated vitamin D milk were used at two quite different dosage levels. Table II shows the types of milks used, the potency desired at the outset, and the potency established on the finished products. The efficacy of the different types of milk as judged by presence or absence of slight rickets will be discussed in detail in another section.

METHOD OF STUDY

Thirteen groups of infants were given an antirachitic substance, either cod liver oil or viosterol (Table I), or some form of vitamin D milk (Table II). The cod liver oil and viosterol were purchased in single lots at the beginning of the study and assayed in the laboratories of the Food and Drug Administration before the actual doses

were determined. The milks* were prepared in the late summer of 1935 by reliable firms under expert supervision. All forms of the milk were evaporated and each was prepared from pooled lots to insure uniformity of product. Assays establishing the potency of the finished products were made also by the Food and Drug Administration, but after the milk had been put into use.

TABLE II

ORIGINAL POTENCY DESIRED AND ACTUAL POTENCY ESTABLISHED FOR VITAMIN D MILKS (EVAPORATED)

PRESCRIBED DURING 1935-36

TYPE OF MILK (EVAPORATED)	AVERAGE NUMBER OF UNITS PER RECONSTITUTED QUART	
	POTENCY DESIRED	POTENCY ESTABLISHED
"Yeast" milk		
1	135	170
2	400	400
Cod liver oil concentrate in milk		
1	135	135
2	400	400
Irradiated milk		
1	135	150
Viosterol in milk		
1	400	400

The daily dose of cod liver oil was measured during the first winter in spoons specially furnished to the mothers for this purpose; during the second winter each daily dose was put up in a separate bottle. Droppers calibrated in the laboratory of the Food and Drug Administration were provided with the viosterol so that the correct amount could be measured with a fair degree of accuracy. During the first year the viosterol was used in a concentrated form, 3 drops containing 1,350 U.S.P. units; for the second year's work the viosterol was diluted until 10 drops contained the same number of units. The chance of error in administration was, therefore, greatly reduced the second year.

The general method of procedure used in selecting infants and in organizing the study was that suggested by Powers and Eliot in 1933.[1] The necessity for making careful selection of the infants for the different groups to be studied was pointed out in this preliminary description of method. Analysis of the current material shows this necessity to be even greater than was believed to exist at that time, especially with respect to color, sex, and rate of growth in length.

When first selected, each group was composed of from 45 to 55 infants, of whom approximately two-fifths were colored and three-fifths, white. Efforts were made to select infants who were born at term and were the result of single pregnancies, who were less than eight

*The cooperation of the Evaporated Milk Association in the preparation of the milks is gratefully acknowledged.

weeks of age on admission to the study and were born after the first of September. Only infants who were artificially fed or breast fed with a supplemental formula containing not less than twelve ounces of milk daily were included in the study. Furthermore, no infant was included for final analysis who was known to have received an appreciable amount of any form of vitamin D previous to admission or an additional form of vitamin D during the period under observation other than that prescribed. Infants were accepted during October, November, December, and in a few cases during the early part of January, and were observed no later than the middle of May. Though the final size of the groups was somewhat reduced by necessary exclusions, there remained at the end a total of 567 infants whose records were suitable for analysis. Of these, 59 per cent were white, 41 per cent colored; 52 per cent were males, 48 per cent, females.

TABLE III

NUMBER OF INFANTS RECEIVING VITAMIN D IN THE FORM OF COD LIVER OIL, VIOSTEROL, OR VITAMIN D MILK CLASSIFIED BY SEX, BY COLOR, BY COLOR AND SEX, AND BY AVERAGE NUMBER OF U.S.P. UNITS OF VITAMIN D TAKEN DAILY AS COD LIVER OIL OR VIOSTEROL OR BY NUMBER OF UNITS PER QUART OF RECONSTITUTED MILK

TYPE OF ANTI-RACHITIC	AVERAGE NUMBER OF UNITS ACCORDING TO COLOR OF INFANTS		TOTAL			WHITE			COLORED		
	WHITE	COLORED	TOTAL	MALES	FEMALES	TOTAL	MALES	FEMALES	TOTAL	MALES	FEMALES
Total			567	297	270	335	183	152	232	114	118
Cod liver oil			163	91	72	90	52	38	73	39	34
	273	274	28	10	18	14	4	10	14	6	8
	460	470	34	17	17	19	10	9	15	7	8
	659	652	74	45	29	40	24	16	34	21	13
	821	789	27	19	8	17	14	3	10	5	5
Viosterol			132	57	75	67	29	38	65	28	37
	686	678	47	20	27	22	8	14	25	12	13
	1,392	1,361	50	20	30	24	10	14	26	10	16
	2,185	2,093	35	17	18	21	11	10	14	6	8
Milk (evaporated)			272	149	123	178	102	76	94	47	47
"Yeast"											
170			52	33	19	34	21	13	18	12	6
400			41	18	23	30	16	14	11	2	9
Cod liver oil concentrate											
135			42	22	20	26	17	9	16	5	11
400			40	26	14	30	19	11	10	7	3
Irradiated											
150			47	27	20	29	15	14	18	12	6
Viosterol											
400			50	23	27	29	14	15	21	9	12

The procedure of examination was the same each year. Observations were made by the same two pediatricians and two public health nurses during the first two years of the study and by a third nurse

who joined the staff during the last year. An x-ray film of the bones of both forearms and a clinical examination were made at the time of admission and at intervals of approximately one month thereafter. Although x-ray readings were made currently, the complete set of films for each of the 567 infants was reviewed at the end of the investigation. The readings for the three years are, therefore, reasonably consistent. The films were classified as "normal" when there was no evidence of rickets, and as "doubtful" when some change appeared to be present but was not sufficiently clear to make a positive diagnosis. When rickets was present, the diagnosis indicated whether the process was very slight, slight, moderate, or marked and whether active, partially controlled, or with healing far advanced. When evidence of rapidly advancing rickets was found, an increase was made in the amount of the antirachitic factor.

The infants were weighed and the crown-heel length was measured in centimeters at each examination. The average monthly increase in length has been estimated for each infant during the total period he was under observation.

MATERIAL STUDIED

Tables III and IV show the general picture as regards number of children, sex, color, and age at admission and at discharge.

Number of Infants Studied.—The number of infants receiving vitamin D in the form of cod liver oil, viosterol, or vitamin D milk grouped according to color and sex and also according to the daily average number of U.S.P. units* taken in the form of cod liver oil or viosterol or to the number of units per quart of reconstituted milk is shown in Table III. It will be noticed that approximately one-half of the infants received vitamin D milk and that a slightly larger proportion was given cod liver oil than viosterol; also that there is a larger percentage of white than of colored infants, especially in the milk groups, and relatively more male than female infants among the white infants, except for those receiving viosterol. It will also be seen that the number of infants receiving a given number of units of any type of antirachitic is small and that, as a result, there is considerable variability in the sex and color of the infants comprising such a group.

*It should be pointed out that the average dosage levels that are used in the tables which follow are not those prescribed, but the average number of units actually taken daily during the total period of observation or up to the time when the first x-ray evidence of rickets appeared. Dosage was classified in U.S.P. units according to certain broad groups as follows:

TYPE OF ANTIRACHITIC	DOSAGE IN U.S.P. UNITS	
	Range	Theoretical Average
Cod liver oil	150-349	250
	350-549	450
	550-749	650
	750-949	850
Viosterol	500-1,099	800
	1,100-1,699	1,400
	1,700-	----

There were 10 infants who received more than 2,299 units of viosterol. The maximum dosage was 2,990.

TABLE IV

AVERAGE AGE IN DAYS AND RANGE ON ADMISSION AND DISCHARGE FOR 567 INFANTS GIVEN VITAMIN D BY TYPE OF ANTIRACHITIC AGENT AND COLOR

TYPE OF ANTIRACHITIC AND COLOR	MEAN AGE (DAYS)		RANGE (DAYS)	
	ADMISSION	DISCHARGE	ADMISSION	DISCHARGE
Cod liver oil				
White	38	199	17-68	150-258
Colored	34	195	15-69	149-276
Viosterol				
White	39	201	17-64	142-262
Colored	39	199	14-69	153-263
Milk (evap.)				
White	38	188	8-63	126-274
Colored	39	186	10-64	122-258

Age at Admission and at Discharge and Period of Observation.—There is still another factor which tends to complicate the problem: The ages of admission and discharge vary considerably, the age of admission from 8 through 69 days of age, discharge from 122 through 276 days. But, nevertheless, as shown in Table IV, the average age at admission and at discharge in the several antirachitic and color groups was about the same, the age at admission being on the average a little over one month and at discharge, about six and one-half months. It should be noted, however, that the infants in the milk groups were discharged about 10 days earlier than those receiving cod liver oil or viosterol.

It would have been preferable, of course, to have examined all of the infants over exactly the same age interval, but as this was not done, the results presented in the following tables are based on the total period of observation for each child. Since a preliminary analysis of the x-ray findings in a shorter period of observation, but one common to all infants (70-139 days) did not show marked differences* with respect to total incidence of rickets between this short interval and the total period of observation, it was decided for the purposes of the present analysis to use the longer but variable interval. If progression of rickets is to be studied or if one is interested in studying the effect on the healing process of several antirachitic agents and dosage levels, it is obviously necessary to use the longer age period. It should be pointed out, moreover, that the incidence of rickets among the infants admitted prior to 35 days of age tended to be less on the average than for infants who were admitted between 35 and 70 days. Some infants who showed no evidence of rickets during the study might have become rachitic had they been observed over a longer and more comparable time interval.

*A criterion of two standard deviations, taking into account the number of degrees of freedom, has been used as the test of statistical significance.

INCIDENCE OF RICKETS

Incidence of Rickets in Total Group

Of the 567 infants studied, the x-ray films of only 10, or 2 per cent, showed an advance in the rachitic process to a moderate or marked degree. In 164 infants, or 29 per cent, rickets was found but did not develop beyond a maximum* of slight or very slight degree. In 103 infants, or 18 per cent, the diagnosis never progressed beyond the doubtful stage.† Two hundred ninety, or 51 per cent, of the infants showed no evidence of rickets throughout the period of observation. The analysis of the data has been directed chiefly toward a study of the incidence of the slighter degrees of rickets and the evidence of advance or regression of the rachitic process during the period of observation.

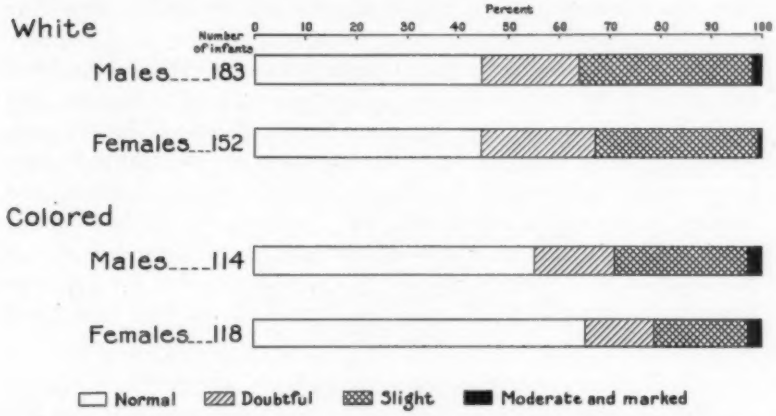

Fig. 1.—Percentage distribution of maximum x-ray findings for 567 infants given vitamin D in the form of cod liver oil, viosterol, or vitamin D milk, by color and sex.

Color and Sex

The incidence of rickets for the males and females in each color group is shown in Fig. 1. A greater percentage of positive cases was found among the white infants than among the colored for both

*The term "maximum diagnosis" will be used to refer to the greatest degree of rickets, whether slight, moderate, or marked, found in an individual infant at any time during the period of observation.

†It is probably of some significance that in 68 per cent of the cases in which a definite diagnosis of rickets was finally made this positive diagnosis was preceded by a "doubtful" diagnosis. This percentage is probably low due to the fact that the interval between x-ray examinations was very variable (anywhere from ten days to two months although the average was approximately one month). In a small group in which the x-ray pictures were taken at intervals of less than a month, all of the first positive diagnoses were preceded by "doubtful" findings. Special study has been made of the x-ray films from which a doubtful diagnosis was made either as a maximum finding in a series or as the finding which preceded a positive diagnosis. It was not possible to find any difference in the appearance of a film classified as doubtful when it preceded a positive or when it occurred alone. The evidence points then to the fact that the so-called "doubtful" diagnoses are in reality the earliest changes to be seen in the x-ray films and their disappearance without further progress of the disease indicates a degree of control that approaches closely that shown by a complete series of normal x-ray films. Further evidence to this effect is found in the fact that the maximum diagnoses of "doubtful" also vary according to the color and sex of the infant as do the maximum diagnoses of "rickets" (Fig. 1 and Table V).

males and females. When the incidence of rickets among colored and white infants is considered, regardless of sex, a significantly larger proportion of positive cases is found among the white infants than among the colored. This picture is the reverse of that which we are accustomed to consider as the usual racial incidence. It should be realized, however, that the well-known difference between white and negro infants is based on the fact that many more negro infants develop rapidly advancing rickets than do white infants. The actual incidence of the earliest stages of the disease might well be the same in the two racial groups or even, as these data demonstrate, reversed. It should be pointed out in this connection, however, that the examinations were all made during the winter when the influence of sunlight was almost negligible, and its absence may be an important factor in the reversal.

There is also a tendency for a larger percentage of cases to occur among the males in a given color group than among the females. But as further analysis indicates that the influence of color is a much more important factor than sex, and since the number of infants in each group would be too small if both sex and color were considered, the detailed tables which follow take only the color of the infants into consideration. In future studies of this type, it would be desirable in the selection of infants to consider sex as well as color, for both factors are fundamental to an understanding of the findings that relate to antirachitic agents and dosage levels.

Antirachitic Substances

With respect to the effect of the different antirachitic substances on the incidence of rickets, analysis of the data has been made first without regard to dosage levels and second taking dosage level into account. Table V shows the incidence of rickets for the total number of white and colored infants given each type of antirachitic substance regardless of dosage level and in addition the incidence in each dosage group.

Efficacy of Antirachitic Substances Regardless of Dosage Level.—Though the findings for the total groups are not based on a large enough number of cases to give throughout results that are statistically significant, nevertheless they do show that the efficacy of the milks (all forms and dosage levels) in preventing rickets is significantly greater than the efficacy of cod liver oil (all dosage levels), in spite of the fact that the average number of units in the milk is considerably lower than that of the cod liver oil. Of the total number of infants receiving vitamin D milks, 53 per cent of the white and 67 per cent of the colored had no rickets as compared with 30 per cent

and 45 per cent, respectively, for white and colored receiving cod liver oil. Moreover, comparison of the milks (using again a combination of all types and dosage levels) with viosterol (all dosage levels) shows exactly the same tendency for the white infants, but the number in the viosterol group is too small and the differences between the incidence of either no rickets or rickets in the two groups are too slight to demonstrate significance. Though viosterol appears here to be more effective than cod liver oil, it should be pointed out that the average number of units taken in the form of viosterol by the total group is considerably in excess of that taken in the form of cod liver oil and direct comparisons cannot be made.

No infants receiving viosterol developed moderate or marked rickets, whereas seven who were given cod liver oil and three who were given vitamin D milks developed these more serious degrees.*

Efficacy of Antirachitic Substances by Dosage Levels.—When attempting to study the different antirachitic substances according to dosage levels certain obvious difficulties are encountered, such as the small number of infants in each dosage group and the unequal distribution according to color and sex. The fact that the dosage levels for the different antirachitic substances are the same in only two instances limits the number of direct comparisons that can be made. Furthermore, the dosages of the antirachitic substances used were not at a sufficiently low level to permit moderate or marked rickets to develop in enough infants to allow advanced rickets to be used as one of the criteria for judging success or failure in the prevention of rickets. However, since the investigation was primarily one of prevention, the proportion of infants showing no evidence of rickets throughout the period of observation and the proportion showing a very slight or slight degree are of basic importance. Though in many

*The color and sex of the infants developing moderate or marked rickets, the type of antirachitic substance used and dosage level are as follows:

CASES OF MODERATE AND MARKED RICKETS

AVERAGE NUMBER OF UNITS (DAILY)	TYPE OF ANTIRACHITIC	MAXIMUM DIAGNOSIS OF RICKETS	COLOR	SEX
135	Vitamin D milk, Cod liver oil concentrate added	Moderate	White	Male
135	Vitamin D milk, Cod liver oil concentrate added	Marked	Colored	Female
150	Irradiated milk	Moderate	White	Male
210	Cod liver oil	Moderate	Colored	Male
251	Cod liver oil	Moderate	Colored	Female
325	Cod liver oil	Marked	Colored	Male
340	Cod liver oil	Moderate	Colored	Female
686	Cod liver oil	Marked	Colored	Male
693	Cod liver oil	Moderate	White	Male
735	Cod liver oil	Moderate	White	Female

instances significant conclusions based on statistical analysis cannot be made because of the small number of infants studied, nevertheless certain consistent and repeated tendencies have been found which are worth presenting.

In the upper section of Table V are shown the findings with respect to the incidence of rickets among the infants given viosterol. There can be seen a general tendency for the incidence of rickets to decrease with increase in dosage. It may be seen that the incidence of rickets is

TABLE V

PERCENTAGE DISTRIBUTION OF MAXIMUM X-RAY DIAGNOSES FOR 567 INFANTS GIVEN DIFFERENT AMOUNTS OF VITAMIN D IN THE FORM OF VIOSTEROL, VITAMIN D MILK, OR COD LIVER OIL, BY COLOR

TYPE OF ANTIRACHITIC	COLOR AND AVERAGE NUMBER OF UNITS PER DAY OR PER RECONSTITUTED QUART	PERCENTAGE DISTRIBUTION			NUMBER OF INFANTS
		RICKETS	DOUBTFUL	NORMAL	
Viosterol	White				
	Total	*37*	*21*	*42*	*67*
	686	46	4	50	22
	1392	33	33	33	24
	2185	33	24	43	21
	Colored				
	Total	*12*	*20*	*68*	*65*
	678	24	16	60	25
	1361	4	23	73	26
	2093	7	21	72	14
Vitamin D Milk (evaporated)	White				
	Total	*28*	*19*	*53*	*178*
	"Yeast" milk				
	170	32	21	47	34
	400	30	10	60	30
	Cod liver oil conc. in milk				
	135	38	27	35	26
	400	17	23	60	30
	Irradiated milk, 150	31	10	59	29
	Viosterol in milk, 400	21	21	58	29
	Colored				
	Total	*22*	*11*	*67*	*94*
	"Yeast" milk				
	170	28	0	72	18
	400	27	27	46	11
	Cod liver oil conc. in milk				
	135	19	19	62	16
	400	30	10	60	10
	Irradiated milk, 150	22	11	67	18
	Viosterol in milk, 400	14	5	81	21
Cod Liver Oil	White				
	Total	*45*	*25*	*30*	*90*
	273	36	21	43	14
	460	37	47	16	19
	659	45	20	35	40
	821	65	12	23	17
	Colored				
	Total	*40*	*15*	*45*	*73*
	274	57	7	36	14
	470	27	27	46	15
	652	41	15	44	34
	789	30	10	60	10

no greater among white or colored infants receiving approximately 1,400 units than among those receiving approximately 2,100 units.

The middle section of Table V gives the findings in regard to vitamin D milks. No very definite conclusions can be drawn concerning the relative efficacy of the different types and doses of antirachitic milks though on the whole it would appear that the higher dosage levels are more effective than the lower in preventing rickets. It may be noted that in each of the white groups receiving 400 units in the form of yeast milk or milk with cod liver oil concentrate or viosterol added and in the group receiving 150 units in the form of irradiated milk, approximately 60 per cent of the infants showed no rickets. The evidence is not as consistent for the colored infants, probably because of the fact that there is a much smaller number of colored infants in each group. Among the infants receiving yeast milk, there is apparently no difference in the incidence of rickets among those receiving the higher dosage (400 units) or the lower (170 units).

In the lower section of Table V are given the findings for cod liver oil. With respect to this group it may be pointed out that the general tendency for the incidence of rickets to decrease with the increase of dosage level again appears for the colored group but with certain inconsistencies. There are even more striking exceptions in the white group. For instance, the white infants receiving the lowest number of units (273) show considerably less rickets than those receiving the highest (821). Of course, there is only a small number of cases in the two groups, 14 and 17, respectively, too few to give any stability to the results, but it will be noticed that the sex distribution of the infants in these two groups is quite uneven and in the opposite direction. Thus, there are only 4 males and 10 females in the lower dosage group; in the higher, 14 males and 3 females (Table III). These contradictory findings may be the result of the fact that the lower dosage level is heavily weighted with females, the higher with males, and that, in addition, the infants of a given sex who developed rickets tend on the average to be growing more rapidly in length than those who did not develop the disease. In other words, in the case of these two cod liver oil groups, the reversal of the general tendency for the percentage incidence of rickets to decrease with increasing unitage may well be related to the factors of sex and growth, a subject that will be discussed more fully in the next section.

Comparisons of Antirachitic Substances at Certain Dosage Levels.—It has been pointed out that direct comparisons of different antirachitic substances at the same dosage level can be made in two instances. These are shown in Table VI. First, a group of white infants given approximately 460 U.S.P. units of vitamin D daily in the form of cod liver

oil is compared with a group including all white infants given milk containing 400 U.S.P. units to the reconstituted quart. The exact number of units consumed by the latter group is not known, but it is presumably somewhat less than 400 units daily. The incidence of rickets is significantly lower among those taking milk, 23 per cent in comparison with 37 per cent for those receiving cod liver oil. The same tendency was found among the colored infants.

TABLE VI

PERCENTAGE INCIDENCE OF RICKETS FOR WHITE INFANTS RECEIVING CERTAIN FORMS AND CERTAIN DOSAGE LEVELS OF VITAMIN D

TYPE OF ANTIRACHITIC	AVERAGE NUMBER OF UNITS PER DAY OR PER RECONSTITUTED QUART	PERCENTAGE INCIDENCE	NUMBER OF INFANTS
Cod liver oil	460	37	19
*Vitamin D milk (evap.)	400	23	89
Cod liver oil	659	45	40
Viosterol	686	46	22

*Includes "yeast," cod liver oil, and viosterol milks.

The second comparison is for two groups of white infants who received cod liver oil and viosterol at approximately the same dosage level, 659 and 686 units, respectively. There is no significant difference in the incidence of rickets among infants given either cod liver oil or viosterol at these levels.

There is no doubt that in the group of white infants studied the milks at the 400 unit level have been more effective in preventing rickets than cod liver oil at the 460 unit level, and the tendency is the same for the colored infants.

No real difference is found in the efficacy of cod liver oil and viosterol for white infants at the 675 unit level. No real superiority of cod liver oil over viosterol or vice versa has been demonstrated at any dosage level.

GROWTH IN LENGTH

The influence of growth in length on the incidence of rickets and its close association with sex has already been suggested. In order to study this question, the average monthly increase in length has been estimated for each infant included in the study. It should be noted that this method of studying growth* differs from the orthodox cross-sectional approach. A series of measurements on each infant observed for a specified age interval is used to estimate that particular infant's average increase in length for the total period he was under observation. Its advantages over the older method have been clearly defined by Boas,[2]

*The relationship between average percentage increase in weight and incidence of rickets has also been investigated, but up to the present time with negative results.

Palmer and Reed,[3] and others. The exact method of analysis is described in detail in a footnote.*

The mean or average of these individual growth rates is shown by color, sex, and by type of antirachitic substance in Table VII. It will

*The method of studying this problem of growth in length consists in estimating the average monthly increase in length for each of the 567 infants. Examination shows that the crown-heel length of an individual infant increases fairly uniformly during early infancy, that is, within the degree of variability of the measurements. Therefore, the straight line, $y = a + bx$, has been taken to describe satisfactory age variations of crown-heel length in the individual infant. The variables, x and y, are respectively age in days, and crown-heel length, measured in centimeters. The b constant is the slope of the line, that is the increase in length per day. The a constant is relatively unimportant, as its value is dependent upon certain arbitrary procedures connected with the solution of the equations. These values have been determined under the least squares criterion. The theory underlying this method is that the observed and theoretical values of y differ by errors which are distributed in accordance with the normal curve.

The b constant multiplied by 30, that is, average increase in crown-heel length measured in centimeters per month, has been used as an index of growth in length. Thus, if 30 b equals 2.38 centimeters, the length of the infant increased on the average 2.4 centimeters per month during the period he was under observation.

The method of determining the constants for the straight line is illustrated for the series of observations given in the following table.

REGRESSION LINE OF CROWN-HEEL LENGTH ON AGE; COLORED FEMALE INFANT (S. C.)

AGE IN DAYS, X	CROWN-HEEL LENGTH IN CM., Y	X^2	XY	
23	50.0	529	1,150.0	
51	53.0	2,601	2,703.0	
79	54.5	6,241	4,305.5	$n = 6$
128	60.0	16,384	7,680.0	$S(x) = 621$
156	61.0	24,336	9,516.0	$S(y) = 341.0$
184	62.5	33,856	11,500.0	$S(x^2) = 83,947.0$
S 621	341.0	83,947	36,854.5	$S(xy) = 36,854.5$

Normal equations:

$$341.0 = 6a + 621\,b$$
$$36,854.5 = 621a + 83,947\,b$$

Solving:

$$b = 0.07935$$
$$30b = 2.380$$
$$a = 48.62$$

and

$$y = 48.62 + 0.07935x$$

Therefore, during the period of observation, that is from 23 through 184 days of age, the crown-heel length of this infant increased from 50.0 to 62.5 centimeters, or approximately 2.4 centimeters (30b) per month (Fig. 2).

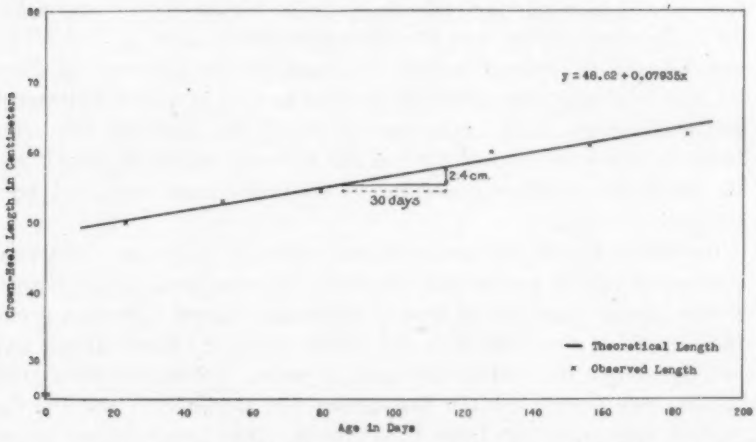

Fig. 2.—Crown-heel length of colored female infant, S. C., measured at irregular intervals from 23 through 184 days of age.

be seen, for example, that the average white male infant grew approximately 2.48 centimeters in length per month during the period he was under observation from one to six and one-half months of age. It should be noted in this connection that these figures are based on observations on a small, highly selected group of Detroit children. It cannot be assumed that the growth rate of infants living in different geographic areas will be the same as those for the Detroit infants included in this study.

TABLE VII

MEAN OF THE AVERAGE INCREASES IN LENGTH (CM.) PER MONTH OF 567 INFANTS GIVEN VITAMIN D IN THE FORM OF COD LIVER OIL, VIOSTEROL OR VITAMIN D MILK (EVAPORATED) BY COLOR AND BY SEX

TYPE OF ANTIRACHITIC AND COLOR	MEAN INCREASE IN LENGTH (CM.) PER MONTH ACCORDING TO SEX	
	MALES	FEMALES
Cod liver oil		
White	2.52 (0.050)*	2.31 (0.086)
Colored	2.54 (0.092)	2.51 (0.106)
Viosterol		
White	2.43 (0.114)	2.26 (0.081)
Colored	2.46 (0.123)	2.34 (0.087)
Vitamin D milk (evaporated)		
White	2.48 (0.047)	2.35 (0.043)
Colored	2.57 (0.089)	2.39 (0.104)
Total		
White	2.48 (0.032)	2.32 (0.029)
Colored	2.54 (0.040)	2.41 (0.045)

*The standard deviation of the mean is shown in parenthesis.

It may be noted that the colored infants tended to grow more rapidly than the white infants of the same sex and that there is a significant difference in the growth in length of the two sexes, the male infants, on the average, growing more rapidly than the female of the same color. As further analysis by type of antirachitic agent shows no real difference between the average increase in length for the infants of a given sex and color who were given any particular type of antirachitic agent and that for the total number of infants of the same sex and color included in the study, only the relation between growth in length and the incidence of rickets according to different dosage levels has been studied.

Growth in Length, Dosage Level and Incidence of Rickets.—The total number of infants was divided, therefore, into two broad, quite distinct dosage groups regardless of type of antirachitic agent. The first group includes those given less than 400 U.S.P. units of vitamin D per day and the second those given 400 units or more. Conservatively stated, the average dosage for the first group was around 275 and for the second, approximately 1,000 U.S.P. units. The lower dosage group includes all those receiving milk and some of the infants receiving cod

liver oil; the upper group, all of those receiving viosterol and some of those receiving cod liver oil.

Table VIII shows for these two dosage groups the percentage incidence of rickets for infants whose growth in length was less than and for those whose growth was the same as or more than that of the average infant of the same color and sex. For the infants in the lower dosage group, less than 400 units, there is no consistent difference in the incidence of rickets between those growing slowly and those growing at a faster rate. On the other hand, the infants in the higher dosage group tended to show a consistent difference: In all cases those infants whose growth in length was less than the average* tended to show a smaller percentage of rickets, those who were growing more rapidly, a higher. This evidence indicates that the lower dosage level may not give enough protection to prevent the development of slight rickets in either the infant whose growth in length is below or above the average, but that the higher dosage does tend to protect much more effectively the infant who is growing slowly than it does the more rapidly growing infant. More detailed study of the whole question is needed before definite conclusions concerning the relationship of growth in length to the incidence of rickets can be drawn.

TABLE VIII

PERCENTAGE INCIDENCE OF RICKETS FOR 307 INFANTS RECEIVING LESS THAN 400 U.S.P. UNITS OF ALL FORMS OF VITAMIN D PER DAY AND 260 INFANTS RECEIVING 400 OR MORE UNITS ACCORDING TO COLOR, SEX AND AVERAGE INCREASE IN LENGTH (CM.) PER MONTH

COLOR, SEX AND AVERAGE INCREASE IN LENGTH (CM.) PER MONTH	PERCENTAGE INCIDENCE OF RICKETS FOR INFANTS RECEIVING		NUMBER OF INFANTS RECEIVING	
	LESS THAN 400 UNITS PER DAY	400 UNITS OR MORE PER DAY	LESS THAN 400 UNITS PER DAY	400 UNITS OR MORE PER DAY
White				
Males				
Increase in length				
Less than 2.45 cm.	40	29	58	35
2.45 cm. or more	26	40	51	39
Females				
Increase in length				
Less than 2.30 cm.	23	39	39	36
2.30 cm. or more	25	52	48	29
Colored				
Males				
Increase in length				
Less than 2.55 cm.	30	21	27	29
2.55 cm. or more	36	30	28	30
Females				
Increase in length				
Less than 2.40 cm.	26	17	31	30
2.40 cm. or more	20	22	25	32

*For white females the difference is significant, for males the tendency is the same but cannot be shown to be significant.

PROGRESS AND REGRESSION OF RICKETS

So far only the maximum findings with respect to rickets have been considered. Study of progress of rickets and of regression or healing also brings out some pertinent facts.

Progress of rickets as demonstrated in x-ray films was considered to be present when an initial diagnosis of "very slight" rickets was followed by a diagnosis of "slight," or when a diagnosis of "slight" progressed to a degree classified as "slight-to-moderate." As has been pointed out, in a few cases the process advanced to "moderate" or to "marked." Obviously such changes can be studied most effectively in the group of infants who were observed at reasonably regular intervals from one to six months of age. One hundred twelve infants were so observed. Of them 46 developed rickets and 21 showed evidence by x-ray of progress or advance in the process. Table IX shows the antirachitic substances that were being given and the number of infants in each color group showing x-ray evidence of rickets and progress of the disease.

TABLE IX

NUMBER OF INFANTS OBSERVED BETWEEN 31 AND 179 DAYS OF AGE, NUMBER WHO DEVELOPED RICKETS, AND NUMBER WHO SHOWED PROGRESSION OF THE DISEASE, BY TYPE OF ANTIRACHITIC AGENT AND COLOR

TYPE OF ANTIRACHITIC AND COLOR	NUMBER OF INFANTS		
	TOTAL	DEVELOPING RICKETS	SHOWING PROGRESSION OF THE DISEASE
Cod liver oil			
White	24	11	7
Colored	19	8	7
Vitamin D milk (evap.)			
White	30	12	1
Colored	12	5	2
Viosterol			
White	15	7	4
Colored	12	1	0
Total			
White	69	30	12
Colored	43	14	9

Detailed information with regard to the 21 infants who showed some increase in the degree of rickets is given in Table X. From these data it would appear that progress occurred most often when cod liver oil was given and least often when vitamin D milks were given. The numbers are too few to attempt detailed analysis, but what evidence there is would seem to be in favor of the milks.

Complete regression or healing was considered to be present when the x-ray films showed that all signs of rickets, even the moderately advanced stages of healing, had disappeared and the bones of the forearms again appeared essentially normal.

TABLE X

INFANTS SHOWING PROGRESS OF RICKETS
(OBSERVED FROM 1 TO 6 MONTHS)

CASE	COLOR	SEX	TYPE OF ANTIRACHITIC AND AVERAGE NUMBER OF UNITS PER DAY OR PER RECONSTITUTED QUART	FIRST DIAGNOSIS	AGE AT FIRST DIAGNOSIS (DAYS)	MAXIMUM DIAGNOSIS DURING PERIOD OF OBSERVATION	AGE AT MAXIMUM DIAGNOSIS (DAYS)
			Cod Liver Oil				
J. S.	W	F	206	A_1	97	A_1+	118
R. W.	C	M	210	A_1-	87	A_2+	176
C. S.	C	M	325	A_1	76	B_2	188
J. I.	C	F	340	A_1	84	A_2	126
P. I.	C	M	463	B_1-	90	B_1	118
N. H.	W	M	481	A_1-	70	A_1	112
G. A.	C	M	661	A_1-	117	B_1+	173
C. F.	C	M	686	A_1	115	A_2	178
A. O.	W	M	693	A_1-	108	A_2	170
J. M.	C	F	702	A_1-	44	B_1	98
M. K.	W	M	766	A_1-	65	A_1	100
W. C.	W	M	799	B_1-	104	B_1	132
L. M.	W	M	810	A_1-	52	A_1	80
R. Y.	W	M	926	B_1-	133	B_1	161
			Vitamin D Milk				
C. M.	C	F	CLO conc. in milk 135	A_1-	85	A_1	99
L. W.	W	F	Yeast milk 400	A_1-	79	B_1	170
W. F.	C	M	CLO conc. in milk 400	B_1	132	B_1+	159
			Viosterol				
R. R.	W	F	581	B_1-	124	B_1	159
V. S.	W	F	1459	B_1-	108	B_2	136
J. V.	W	F	2300	A_1-	92	A_1	134
L. S.	W	M	2869	A_1-	86	A_1+	115

Code: A_1-, $B-_1$, very slight; A_1, B_1, slight; A_1+, B_1+, "slight to moderate"; A_2, B_2, moderate; A_3, B_3, marked. A indicates active rickets; B, under control.

In studying this regression or healing, it became evident that the same factors which enter into the problem of the incidence of slight rickets also influence its disappearance. Dosage level appears to be the most important factor, with sex playing a somewhat more important rôle than it does in the development of the disease. For comparative studies of healing, three distinct, narrowly limited dosage levels were selected: one averaging approximately 150 units, another 400 units, and the third 675. The lower dosage group is composed of infants given the three forms of vitamin D milk at the lower levels, the middle one of infants given vitamin D milk at the higher level, and the third one of infants given viosterol or cod liver oil at the specified level.

TABLE XI

PERCENTAGE INCIDENCE OF HEALING AMONG INFANTS RECEIVING COD LIVER OIL, VIOSTEROL OR VITAMIN D MILKS AT SPECIFIED DOSAGE LEVELS BY COLOR

TYPE OF ANTIRACHITIC AND COLOR	AVERAGE NUMBER OF UNITS PER DAY OR PER RECONSTITUTED QUART	PERCENTAGE OF CHILDREN DEVELOPING RICKETS, WHOSE X-RAY FILMS SHOWED COMPLETE HEALING AT DISCHARGE	PERCENTAGE INCIDENCE OF RICKETS	NUMBER OF INFANTS RECEIVING SPECIFIED TYPE OF ANTIRACHITIC
Cod liver oil				
White	*677	21	42	33
Colored	*662	27	37	30
Viosterol				
White	686	50	46	22
Colored	678	50	24	25
Vitamin D milk (evap.)				
†Lower level				
White	153	27	34	89
Colored	152	17	23	52
‡Higher level				
White	400	50	23	89
Colored	400	33	21	42

*The range of the number of units administered is less than for the group receiving approximately 659 units of cod liver oil, shown in Table V.

†Includes "yeast," cod liver oil concentrate, and irradiated milks.

‡Includes "yeast," cod liver oil concentrate, and viosterol milks.

Table XI shows the type of antirachitic agent, the three major dosage level groups, and the percentage of rachitic infants in whose x-ray pictures complete healing was seen at discharge; it also shows for comparison the total incidence of rickets in each group. The following facts are apparent.

The vitamin D milks at the lower dosage levels (150 units) do not appear to be as effective *in bringing about healing* as the milks at the higher level (400 units) or as viosterol at 675 units. This is of definite interest, since *with respect to the prevention* of rickets the milks, even those of the lower dosage levels, tend (as has been pointed out before) to be at least, if possibly not more, effective than 675 U.S.P. units of viosterol or cod liver oil.

Though the infants in the cod liver oil group were receiving the same number of units as those on viosterol, nevertheless they show a tendency to heal less promptly than did those on viosterol.

The superiority of the milks of the higher dosage level and of viosterol is again brought out.

In Table XII further analysis is made of the effect on healing of the different types of milk at different dosage levels. Milk with added viosterol (400 units) shows a definite superiority over other types of milk containing 400 units ("yeast" and cod liver oil concentrate milk). If these data are compared with those on Table XI, showing the percentage of healing that occurred when viosterol was given alone in doses of approximately 675 units daily, it will be seen that the milk containing 400 units of viosterol appears to be more efficient in bringing about regression of this slight rickets than viosterol when given alone at an even higher level.

TABLE XII

PERCENTAGE INCIDENCE OF HEALING AMONG INFANTS RECEIVING VITAMIN D MILK IN DIFFERENT FORMS AND DOSAGE LEVELS BY COLOR

TYPE OF MILK, NUMBER OF UNITS PER RECONSTITUTED QUART AND COLOR	PERCENTAGE OF CHILDREN DEVELOPING RICKETS, WHOSE X-RAY FILMS SHOWED COMPLETE HEALING AT DISCHARGE	PERCENTAGE INCIDENCE OF RICKETS	NUMBER OF INFANTS RECEIVING SPECIFIED TYPE OF MILK
Vitamin D milk (evaporated)			
"Yeast" milk			
170			
White	36	32	34
Colored	0	28	18
400			
White	44	30	30
Colored	0	27	11
Cod liver oil concentrate in milk			
135			
White	30	38	26
Colored	33	19	16
400			
White	40	17	30
Colored	33	30	10
Irradiated milk, 150			
White	11	31	29
Colored	25	22	18
Viosterol in milk, 400			
White	67	21	29
Colored	67	14	21

COMMENT

In the analysis of the data presented in this study the statistical method has been applied. Though the individual groups of infants at each dosage level were too small to be able to test the reliability of the results in many cases, nevertheless the tendencies shown in the

data have been consistent and repeated with but few exceptions. In a fair proportion of cases the data have been adequate to permit tests for statistical significance, and the results so obtained uniformly strengthen the conclusions to be drawn from the general tendencies shown by the data as a whole. The differences that have been shown to exist with respect to the incidence of rickets and healing between white and colored infants, and between the less rapidly and the more rapidly growing infants make it clear that, for each dosage level studied, color and sex should both have been considered in selection of the groups, and enough infants should have been included so that growth in length could have been classified more specifically.

The problem of growth as related to rickets needs to be studied further, as, for instance, the question of whether growth in length during the early months of life is related to length at birth and whether rate of growth may be predicted from measurements at birth. Additional study is needed to determine more satisfactorily whether the several available types of antirachitics are equally effective in the more rapidly growing infants, and whether the basic factors entering into the regression or healing of slight rickets are the same as those influencing the healing of moderate or marked rickets and if so whether their relative importance remains the same.

The conclusions that can be reached as a result of the analysis are included in the following summary.

SUMMARY

1. This paper reports an investigation of the relative efficacy of several different forms of vitamin D at different dosage levels. The study was carried out in Detroit, Mich., during the winter months of 1933-36. Five hundred sixty-seven full-term infants were observed from approximately one through six and one-half months of age. They were given either cod liver oil or viosterol or some form of vitamin D milk at different dosage levels. The dosage administered varied considerably, from approximately 150 through 3,000 U.S.P. units. Diagnosis was based on x-ray films of the bones of both forearms, taken at approximately monthly intervals.

2. The results of this study have demonstrated the necessity of considering such factors as color, sex, rate of growth in length, period of observation, and interval between examinations as basic when attempting to evaluate the efficacy of certain types of antirachitic substances administered at different dosage levels in the prevention of rickets.

3. The evidence presented refers almost exclusively to the incidence of slight rickets as the dosage level was sufficiently high to prevent the development of moderate or marked rickets except in a few infants.

4. The incidence of rickets was significantly less among the colored infants than among the white. The same tendency was found consistently among infants given the different antirachitic agents both when all dosage levels were combined and, with few exceptions, at the different dosage levels.

5. When pertinent basic factors were taken into consideration, it became apparent that, in spite of their lower dosage level, the milks, especially those at the 400 unit level, tended to be more effective in the prevention of rickets than cod liver oil. There is also evidence that viosterol is at least as effective as cod liver oil, and no evidence that cod liver oil is superior to viosterol, unit for unit, in the prevention of rickets.

6. There is no definite evidence from this study that one type of milk at the 400 unit level is superior to another in the prevention of rickets. For the lower dosage levels no clear-cut conclusions with regard to comparative efficacy can be drawn.

7. Within the dosage range used for each type of antirachitic, the higher dosage levels appear to be more effective, provided the basic factors mentioned above are taken into consideration.

8. Advance in the rachitic process occurred most frequently in infants receiving cod liver oil, least frequently in those given vitamin D milk.

9. Regression or healing of the slight degrees of rickets discussed in this paper tended to occur more promptly in infants receiving vitamin D milk of the higher (400 units) dosage level than in those receiving that of the lower level (150 units). Of the different types of vitamin D milk containing 400 units, that to which viosterol was added appeared to be the most efficient. This form also tended to be more efficient than viosterol alone even when the latter was given at a somewhat higher level. When given at a dosage level of approximately 675 units, viosterol tends to bring about regression of slight rickets more promptly than cod liver oil at the same dosage level.

10. The incidence of slight rickets has been shown to be closely and consistently related to growth in length when the dosage of the antirachitic is relatively high, whereas for infants in the lower dosage group there is no consistent difference in the incidence of rickets. These findings indicate that at the higher level the balance between rickets-producing and rickets-preventing factors has been stabilized to such an extent as to allow rate of growth in length to become evident. On the other hand, when a smaller amount is given, the effect of the growth in length is lost in the stronger influence of the inadequate amount of vitamin D.

11. It would appear that if rickets is to be prevented or promptly controlled an amount of vitamin D must be given that will assure

stability in the metabolic processes providing for normal bone growth and allow an adequate margin of safety for the rapidly growing infant. From the data here presented, this amount would appear to be at least as high as that contained in the usual dose of cod liver oil; namely, two to three teaspoonfuls.

Finally in evaluating the results of such a study as this one, it should be borne in mind that from the public health point of view, as well as that of the individual infant, the value of a substance containing vitamin D should be measured first in terms of success in the prevention of rickets under practical conditions and second in terms of economy, and that such economic considerations must include not only the cost of the vitamin but also the need and cost of other nutrients supplied by the vehicle carrying vitamin D.

REFERENCES

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2. Boas, F.: The Growth of Toronto Children. United States Bureau of Education, Report of the Commissioner of Education, 1896-1897, Vol. 2, Government Printing Office, Washington, D. C., pp. 1541-1599.
3. Palmer, C. E., and Reed, L. J.: Human Biology **7**: 319, 1935.

American Academy of Pediatrics

Proceedings

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES

Contagious Disease Hospitals

Part II

THE second report concerns contagious hospitals found in Regions II and IV of the American Academy of Pediatrics. Six hospitals are represented from the South and seventeen from the Far West. Sixteen of the total number are contagious divisions of general hospitals. Questionnaires were filled out and returned to the committee by the following hospitals.

HOSPITAL NUMBERS. SECTIONS II AND IV. EXHIBIT A

Section II

NO.	
1	Municipal Hospital, Atlanta, Georgia
2	City Hospital, Louisville, Kentucky
3	Knoxville General Hospital, Isolation Dept., Knoxville, Tennessee
4	Memphis General Hospital, Isolation Dept., Memphis, Tennessee
5	John Sealy Hospital, Contagious, Galveston, Texas
6	Henry A. Wise Hospital, Norfolk, Virginia

Section IV

NO.	
1	San Luis Obispo General Hospital, San Luis Obispo, California
2	Riverside County Hospital, Riverside, California
3	Los Angeles County Hospital, Los Angeles, California
4	No reply
5	San Diego County General Hospital, Contagious Department, San Diego, California
6	San Bernardino County Charity Hospital, San Bernardino, California
7	Santa Barbara General Hospital, Santa Barbara, California
8	Alameda County Hospital, Oakland, California
9	Children's Hospital, Contagious Dept., San Francisco, California
10	City and County Hospital, Contagious Dept., San Francisco, California
11	Santa Clara County Hospital, Isolation Dept., San Jose, California
12	Sacramento County Hospital, Isolation Dept., Sacramento, California
13	Fresno County Hospital, Isolation Dept., Fresno, California
14	Portland Isolation Hospital, Portland, Oregon
15	Salt Lake General Hospital, Salt Lake City, Utah
16	City Contagious Hospital, Tacoma, Washington
17	Isolation Hospital with Firlands Tuberculosis Sanitorium, Seattle, Wash.
18	Rivercrest Hospital, Spokane, Washington

As far as the committee is able to determine, the list represents the only hospitals which may be classified as contagious with the possible exception of one hospital in California and one in Georgia from which no questionnaires were returned.

I. Staff

A. Professional Staff

1. Attending Staff

EXHIBIT B

A. PROFESSIONAL STAFF. I. STAFF. 1. ATTENDING STAFF

HOSP. NO.	ALL PATIENTS UNDER CARE OF PHYS. ON STAFF	ALL PHYSICIANS IN COMMUNITY ALLOWED TO HAVE PATIENTS IN WDS. AND TREAT THEM	QUALIFICATIONS OF OUTSIDE PHYSICIANS	PEDIATRICS				OTOLARYNGOLOGY				ORTHOPEDICS				OPTHALMOLOGY			
				SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REG. INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REG. INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REG. INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REG. INTERVALS	ON CALL ONLY
Section II																			
1	Yes	No	Spec. arrangement with hosp. supt.	Yes 19	1 for 12 6 for 3 12 for 1	Yes Yes	Yes	Yes 18	18 for 3 mo.	9 Yes	9 Yes	Yes 8	6 for 12		Yes	Yes 10	3 for 12		Yes
2	Yes	No	None	Yes 6	2 mo.	Pediatrists	Spec.	Yes 6	2 mo.			Yes 6	2			Yes 6	2		
3	No pay pts. have choice	Phys. of pay cases	Good standing	Yes	2-3	Yes		Yes	2-3	Yes		Yes	2-3	Yes		Yes	2-3	Yes	
4	Yes	Yes		Yes	12	1-3 daily		Yes	12	Yes		Yes	12	Yes		Yes	12	Yes	
5	Yes	No	Staff members	Yes 2	Serve continuously			Yes 1	Serve continuously			Yes 1	Serve continuously			Yes 1	Serve continuously		
6	No	Yes		No				No				No				No			
Section IV																			
1	Yes	No																	
2	Yes	No			12					Yes					Yes			Yes	

EXHIBIT B—CONT'D

EXHIBIT B—CONT'D

3	Yes	No		Yes 8	6	Yes		Yes 2	12	Yes		Yes			Yes	Yes			Yes
5	Yes Pay	No Private	Cases able to Dr.	Yes 6	2	Yes		Yes			Yes	Yes			Yes	Yes			Yes
6	Yes	Private only in cont.		Yes 2	6	Yes		Yes		Yes		Yes 2	6	Yes		Yes		Yes	
7	Yes	No		Yes 2	6	Yes		Yes 3	4	Yes		Yes 1	12	Yes		Yes 1	12	Yes	
8	Yes	None	None	Yes 5				Yes 8				Yes 9				Yes 4			
9	Yes	No		Yes	12	Yes		Yes			Yes	Yes			Yes	Yes			Yes
10	Yes	Send but not treat					Yes				Yes				Yes				Yes
11	No	No		Yes 3		Yes		Yes 2		Yes		Yes 1		Yes		Yes 1		Yes	
12	Yes	No Only staff mem. allowed		Yes 2	6	Yes		Yes 1	12	Yes		Yes 3	4	Yes		Yes 1	12	Yes	
13	Yes	No		Yes 1	12		Yes	Yes 4	12		Yes	Yes 1	12		Yes	Yes 4	12		Yes
14	No	Yes		Yes	12	Yes													
15	No	Yes		Yes 1	12	Daily	Cont. and T.B.	Yes 4	3		Yes	Yes 6	2		Yes	Yes 4	3		Yes
16	Yes	Yes		County Medical Society gives consultation when needed															
17	Yes	No	May as Consultant Mem. King Co. Med. Soc.	Yes 1		Once wk. and call		Yes 1		Once wk. and call		Yes 1		Once wk. and call		Yes 1		Once wk. and call	
18	No Attending Staff—City Health Officer in complete charge																		

EXHIBIT B

A. PROFESSIONAL STAFF. I. STAFF CONTINUED. 1. ATTENDING STAFF

HOSP. NO.	SURGERY				NEUROLOGY				PSYCHIATRY				PSYCHOLOGY				DERMATOLOGY			
	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY
Section II																				
1	Yes 30	3-12		Yes	Yes 4	6-12		Yes	Yes 1	12		Yes	Yes 1	12		Yes	Yes 2	12		Yes
2	Yes 6	2			Yes 6	2			Yes 6	2			Yes 6	2			Yes 6	2		
3	Yes	2-3	Yes		Yes	2-3	Yes		Yes	2-3	Yes		Yes	2-3	Yes		Yes	2-3	Yes	
4	Yes	12	Yes		Yes	12	Yes		No				No				Yes	12	Yes	
5	Yes 1	Serve continuously			Yes 2	Serve continuously			Yes 1	Serve continuously			No				Yes 2	Serve continuously		
6	No				No				No				No				No			
Section IV																				
1	Yes 4	3	Yes																	
2			Yes					Yes												
3	Yes			Yes	Yes			Yes	Yes			Yes	N.R.				Yes			Yes

EXHIBIT B—CONT'D

5	Yes			Yes	Yes			Yes	Yes			Yes	No				Yes			Yes
6	Yes		Yes																	
7	Yes 3	6	Yes		Yes 1	6	Yes		Same Dr. as Neurology				No							
8	Yes 28				Yes 4				Yes	Same as Neurology			No				Yes 4			
9	Yes			Yes	Yes			Yes	Yes			Yes	Yes			Yes	Yes			Yes
10				Yes				Yes				Yes				Yes				Yes
11	Yes 1			Yes	No				No				No				Yes 1			Yes
12	Yes 12	4	Yes		Yes 1	12	Yes		Yes 1	12	Yes		Same as Psychiatry				Yes 1	12	Yes	
13	Yes 3	12		Yes	Yes 1	12		Yes	Yes 1	12		Yes	Yes 1	12		Yes	Yes 1	12		Yes
14	No reply																			
15	Yes 12	4		Yes	Yes 1	12		Yes	Yes 1	12		Yes	No				Yes 3	4		Yes
16	County Medical Society gives consultation when needed																			
17	Yes 1		Once wk. and call		If necessary			Yes	If necessary			Yes	If necessary			Yes	If necessary			Yes
18	No Attending Staff—City Health Officer in complete charge																			

EXHIBIT B

A. PROFESSIONAL STAFF. I. STAFF CONTINUED. 1. ATTENDING STAFF

HOSP. NO.	DENTISTRY				ORAL SURGERY				ORAL HYGIENE				ROENTGENOLOGY				PATHOLOGY			
	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY
Section II																				
1	Yes 2	12		Yes	Yes 2	12		Yes	Yes 2	12		Yes	Yes 1	12			Yes 1	12		
2	Yes 6	2			Yes 6	2			Yes 6	2			Yes 6	2			Yes 6	2		
3	Yes	2-3	Yes		Yes	2-3	Yes		Yes	2-3	Yes		Yes	2-3	Yes		Yes	2-3	Yes	
4	Yes	12	Yes		Yes	12	Yes		No				Yes	12	Yes		Yes	12	Yes	
5	Yes 1	Serves continuously			Yes 1	Serves continuously			Yes 1	Serves continuously			Yes 1	Serves continuously			Yes 1	Serves continuously		
6	No				No				No				No				No			
Section IV																				
1													Yes 1	12	Yes					
2			Yes								Yes		*	12						
3	N.R.				Yes			Yes	N.R.				Yes			Yes	Yes 2	12		

EXHIBIT B—CONT'D

5	Yes			Yes	Yes			Yes	No				Yes			Yes	Yes			Yes
6	Yes 3	On at same time	Yes										Yes 1	12	Yes		Yes 1	12	Yes	
7	Yes 1	12	Yes		Yes 1	12	Yes		Same Dr. as Oral Surgery				Yes 1	12	Yes		Yes 1	12	Yes	
8	Yes 1				Yes 3				Yes 1				Yes 3				Yes 5			
9	Yes			Yes	Yes			Yes	Yes			Yes	Yes			Yes	Yes			Yes
10				Yes				Yes				Yes				Yes				Yes
11	Yes 1		Yes		No				No				Yes 1		Yes		No			
12	Yes 1	12	Yes		Yes 1	12	Yes						Yes 2	6	Yes		Yes 1	12	Yes	
13	Yes 1	12		Yes	Yes 1	12		Yes					Yes 1	12		Yes	Yes 1	12		Yes
14																				
15	Yes 2	6		Yes	No				No				Yes 1	12	3 days wk.		Yes 1	12	Daily	
16	County Medical Society gives consultation when needed																			
17	Yes 1		Daily and call		Yes 1			Yes	Yes 1			Yes	Yes 1		Daily		If necessary			Yes
18	No Attending Staff—City Health Officer in complete charge																			

EXHIBIT B

A. PROFESSIONAL I. STAFF CONTINUED

HOSP. NO.	ALLERGY				TIME		SALARY	
	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	ANY ON FULL?	THOSE ON FULL	ANY ON SALARY?	THOSE ON SALARY
Section III								
1	Yes	12		Yes	Yes	Medical Supt. Prof. Med. & Surg. Pathologist Roentgenologist	Yes	Those on full time
2	Yes 6	2			Yes	1	Yes	2
3	Yes	2-3	Yes		No		No	
4	No				No		No	
5	Yes 1	Serve continuously			Yes	Pathology 1 Surgery 2	Yes	All
6	No				No		Yes	City Physician
Section IV								
1					No		Yes	Roentgenology
2					No		No	
3	Yes			Yes	No		N.R.	
5	No				Yes	Chief of Dept. Tuberculosis	Yes	County Psychiatrist

EXHIBIT B—CONT'D

HOSP. NO.	ALLERGY				TIME		SALARY	
	SPECS. ON STAFF	NO. MO. EACH YR.	VISITS AT REGULAR INTERVALS	ON CALL ONLY	ANY ON FULL?	THOSE ON FULL	ANY ON SALARY?	THOSE ON SALARY
Section IV—Cont'd.								
6	Yes 1	12	Yes		No		Yes	Pathologist Roentgenologist
7	N.R.				No		No	
8	No				No		Yes	X-ray Pathology
9	Yes			Yes	No		No	
10				Yes	Yes		Yes	Director $4,200 yearly
11	Yes 2		Yes		N.R.		Yes	Roentgenology $100 per month
12					No		No	
13					No		Yes	$50 per month
14					Yes	City Health Officer	Yes	All City Health Officers
15	Yes 1	12		Yes	No		Yes	2 Med. Drs. part time
16					No		Yes	Director of Health Supt. of Hosp.
17	No				Yes	Infec. Dis. Specialist	Yes	All
18	No Attending Staff—City Health Officer in complete charge							

Among 23 hospitals 17 report that ward patients are under the exclusive care of the attending staff. Only 6 hospitals permit all physicians in the community to send patients to their wards and treat them there. All of the hospitals require that their men be of good standing in their community.

Information concerning physicians on the attending staff in the various specialties is presented in Exhibit B.

None of the hospitals has a full-time staff. Seven report that one or two members of the staff are employed full time. The city health officer is placed in this category in one instance. Fifteen report that one or more members of the staff are paid a salary. This usually applies to individuals in charge of the x-ray department or the laboratories or to a health officer.

Resident Staff.—Eighteen hospitals employ resident physicians. In 6 instances more than one is employed. Women are eligible for this position in 10. All pay the resident a salary. This varies from $50.00 to $200.00 per month; 14 hospitals pay a salary to the resident of more than $50.00 a month. Twelve hospitals require that the resident have at least one year or more of previous hospital experience. Two require more than one year, and the remainder are content with no previous experience except an M.D. degree from a class A school. The length of the service is usually six months or one year, just four services are for one year. The resident has dispensary duties in seven instances. Three hospitals did not reply to this question.

Six hospitals employ assistant residents, women being eligible in four. All pay the assistant resident a salary. Four require previous hospital experience in order for one to qualify for the position. The length of the service is six months in one hospital, one year among the others. Dispensary duties are available in three instances.

Sixteen hospitals employ internes, twelve more than one, and eight more than two. Seven have eight or more. None have more than nineteen. Women are eligible in eight. Fourteen pay a salary to internes. This is usually $25.00 or less per month. Among fifteen hospitals which replied, only one requires previous hospital experience in order to qualify for interneship. All require an M.D. degree from an accredited school. The length of the service varies from 20 days to one year. One-year services are available in eight instances; among the others the service is for three months or less.

Educational Activities.—These are presented in chart form (Exhibit C).

Nine of the 23 hospitals in Regions II and IV are connected with medical schools, 4 among 6 in Region II and 5 among 17 in Region IV. In all but one of these, clinics are available to medical students. Ward rounds are offered for medical students in 7. One did not reply. Eight hospitals have clinics open to practicing physicians, and they may attend ward rounds or walks in 9. Fourteen hospitals hold regular clinical conferences and 16 hold similar pathological conferences, which are usually held weekly. Eleven hospitals have available facilities for research and 8 encourage research in communicable disease.

Special Information.—Presented in Exhibit D with summary following.

Thirteen hospitals report that new cases may be placed in observation wards, cubicles, or one and two bedrooms until the diagnosis is certain. Routine cultures for diphtheria are taken on admission in 14 hospitals, for hemolytic streptococci in 8. Routine vaginal smears are done in 8 hospitals, Von Pirquet or Mantoux tests in 4, Wassermann or Kahn tests in 13, Schick tests in 3, Dick tests in 2. Routine

EXHIBIT C

EXHIBIT C

EDUCATIONAL ACTIVITIES

HOSP. NO.	MEDICAL SCHOOL IN CONNECTION WITH HOSP.	MEDICAL CLINICS GIVEN	STUDENTS WARD ROUNDS WALKS GIVEN	PRACTICING PHYSICIANS		POST-GRADUATE COURSES
				NO. AND CHARACTER CLINICS OPEN TO	NO. AND CHARACTER WARD ROUNDS OPEN TO	
Section II						
1	Emory Univ.	Yes	Yes	None	None	No
2	Med. Dept., Univ. of Louisville	Frequently	Regularly	Yes—Cont. cases not suitable for gen. clinics	Yes—Daily ward walks. Not often by outside phys.	No
3	None	Yes Internes	Yes	Yes—Out-patient clinic	Yes	No
4	Univ. of Tennessee	Yes	Daily	None	Yes—Any time they desire	No
5	Med. Dept., Univ. of Texas	Yes	Yes	None	None	No
6	None	None				
Section IV						
1	None	None	None			No
2	None					No
3	Univ. of California	Yes	Yes	1 per wk. case demonstration and lectures	N.R.	No
5	None			None	Not in cont. section	No
6	None	N.R.	N.R.	Charity cases for staff men only	N.R.	No
7	None	No	No	Weekly conferences	No	No
8	None	No	No	Surgical medical	Medical and surgical	No
9	Univ. of California	Semimonthly	N.R.	Semimonthly	Daily if desired	No
10	Univ. of California and Standard Med. School	Yes	Yes	None	Yes—No regular schedule	No
11	None			None	None	No
12	None			None	None	No
13	None			None	None	No
14	Univ. of Oregon	Yes	Yes	None	N.R.	No
15	Univ. of Utah Med. School	No	No	Staff-periodic interval	Salt L. Co. Med. Soc. and Utah St. Med. Assn. Mem.	No
16	None	None	None	N.R.	N.R.	No
17	None	None	None	No	Yes—Variable	No
18	None			No	No	No

EXHIBIT C

EDUCATIONAL ACTIVITIES

HOSP. NO.	INTERNES		LIBRARY	FACILITIES FOR RESEARCH AVAILABLE TO RESIDENT AND HOUSE STAFF	ENCOURAGE RESEARCH COMMUNICABLE DISEASES
	CLINICAL CONFERENCES HELD AND HOW OFTEN?	PATHOLOGICAL CONFERENCES HELD AND HOW OFTEN?	NO. VOLUMES IN HOSP. MED. LIBRARY		
Section II					
1	Monthly regular interne Cont.	Weekly entire hosp. staff	550	Use of clinical material and lab. assistance of visiting men and pathologist	No
2	Weekly	As available	Small No.	None	No
3	Monthly	Weekly	? on No.	Yes	Yes
4	Yes—Occasionally	Almost 6 yearly	None	Clinical experiments with serum vaccines and medications	Yes
5	No	Weekly	None	None	No
6					
Section IV					
1			30		
2			300		
3	3 per week	1 per week	Yes	Bacteriological Lab. in Com. Dis. Hosp.	
5	Weekly	Weekly	300	Only on individual effort	No
6	Yes	Yes	325	N.R.	N.R.
7	1 per week	1 per week	50	Limited amount. Study of vascular abnormalities and arteriograms	No
8	Every week	Every week	Co. Med. Soc. Library	To limited extent only	Yes
9	N.R.	N.R.	500	Yes	Yes
10	Daily	Weekly	Being revised	Yes	Yes
11	Semiweekly	At autopsies	100	Nothing special	No
12	No	Weekly	322	None	No
13	Daily ward walks	Weekly	1,000	None	No
14	No	No	No	None	No
15	1 every 2 months	1 every 2 months	No	None	Yes
16	No	No	15	Connected with City Health Dept.	Yes
17	1 per week	Yes	100-125	Well-equipped laboratory with technicians	Not discouraged
18			No	None	Yes

blood counts are taken in 17 hospitals, urinalyses in 18, complete histories are taken and physical examinations are done in 18 hospitals. Five did not reply to this section.

II. Superintendent

This section of the questionnaire concerns the physical set-up of the hospitals. Twenty-two hospitals replied. Among that number only 3 are found in poor residential, tenement and factory districts. The remainder are located in better or moderate, residential, apartment, and shop districts. Only 5 report that their neighborhood is noisy as a result of the presence of factories, trolleys, heavy traffic, or railroads.

Exhibit E presents certain details concerning the physical organization, size, etc., of these hospitals.

Twelve hospitals have one building, 3 have 5, and 2 have 6 buildings. The earliest construction date is 1910, the latest, 1934. First buildings were constructed between 1910 and 1920 for 11 hospitals. First buildings were constructed in 1920 or later among 6. First buildings for 2 after 1930. Nine hospitals have only one or two floors (5-2, 4-1). Six are of fireproof construction. Cost of buildings again shows great variation—from $4,500.00 to $1,000,000, depending on the size and modernity of the plant. Only 11 hospitals supplied the latter information, and among these 6 cost less than $100,000.00.

Bed capacities among 20 hospitals which replied vary from 14 to 456. Only 6 have bed capacities of less than 50. Nine have 100 or more. The three largest report 456, 423, and 350. The three smallest, 14, 18, and 30. Eighteen hospitals report the number of cribs available, which varies from 2 to 26. The three highest report 26, 24, and 22; the lowest, 2, 2, and 2.

Among 19 hospitals which replied, 17 have wards and 8 have cubicles available. These may contain from one to four beds in different hospitals.

Fourteen hospitals exclude no contagious disease; four exclude pertussis, measles and chickenpox; and ten exclude syphilis, one, typhoid fever and the dysenteries.

Seven hospitals did not reply to the question concerning observation wards. Among 15 which replied, 9 do not have them. Three have roms or cubicles which can be used in this capacity.

Contagious Disease Wards (Exhibit F).

Fifteen replies were received to this section of the questionnaire. Fourteen hospitals have contagious disease wards. These vary from one to eight in number. Ten hospitals have 3 or more wards. The total number of beds, of course, varies considerably depending upon the size of the hospital. The lowest number is 3, the highest, 500; but only 3 report a bed capacity of 100 or more. Nine of the 15 hospitals report fewer than 50 beds. Wards for the most part are not large; only one hospital reports 20 or more patients to a ward; the remainder report from 2 to 16. Five hospitals have cubicles and 12 separate rooms. All report that the hospital gets sunlight and 9 have outdoor porches. Adults and children are admitted to the same ward in 10 hospitals.

Admissions.—Admission figures and other relative information for hospitals listed by number for the years 1932, 1933, and 1934 are presented in Exhibit G.

Only three hospitals report admissions of 5,000 or more for any one of the three years considered. Many report fewer than 1,000 admissions. Total admissions for all hospitals is not large when the size of the area involved is considered. Percentages of deaths for all hospitals were 6.2, 6.4 and 7.7 for the years 1932, 1933, and 1934, respectively.

EXHIBIT D

SPECIAL INFORMATION. I. STAFF

HOSP. NO.	OBSERVATION WARDS			PROCEDURES BEFORE ADMISSION TO WARDS										
	WARDS	TIME CASES IN OBSERVATION	TIME CASES MAY BE KEPT	THROAT CULTURE B. DIPH.	THROAT CULTURE HEMOLYTIC STREPT.	VAGINAL SMEARS FOR GON.	VON PIRQUET OR MANTOUX	WASSERMANN OR KAHN	SCHICK TEST	DICK TEST	ROUTINE BLOOD COUNTS	URINALYSIS	HISTORY TAKEN	COMPLETE PHYSICAL MADE
Section II														
1	Yes Rooms	Diag. is certain	Discretion of staff	Yes	No	Yes	As indicated	Taken later	As indicated	No	Yes	Yes	Yes	Yes
2	No to cont. hosp.			Yes	Yes		Man.	Wass.	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Attending Drs. judgment		Yes	Yes	Yes	Man.	Kahn	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes		As long as necessary until diag. is made	On all	On all	All formulas	Yes	Wass.	Yes	No	Yes	Yes	Yes	Yes
5	Yes	48 hr.		Yes	Yes	If discharge or inflammation is present	Yes	Wass.	Yes	No	Yes	Yes	Yes	Yes
6														

EXHIBIT D—CONT'D

Section IV

1				No	No	No	No	Kahn	No	No	Yes	Yes	Yes	Yes
2	Yes	As directed by Attending Dr.	As directed by Dr. until diag. is established	Yes	Yes	Not routine	Not routine	Yes	Not routine		Yes	Yes	Yes	Yes
3	Yes			Yes	No	Yes	No	Children no Adults yes	No	No	Yes	Yes	Yes	Yes
5	Cubicles only			Yes	No	If indicated	As ordered	As ordered	As ordered	As ordered	Yes	Yes	Yes	Yes
6	Not admitted for observation													
7	None			As indicated		As indicated		Yes	As indicated		Yes	Yes	Yes	Yes
8	None			Yes	Yes	Yes	Not regular	Yes	Not regular		Yes	Yes	Yes	Yes
9	Yes	24 hr.	Until diag. is made	No	If indicated	No	Routine	Routine			Yes	Yes	Yes	Yes
10	None Cubicle or separate room	10-24 days		2-48 hr. intervals	2-48 hr. intervals	3-5 day intervals	No	Both	Not regular	No	Yes	Yes	Yes	Yes

EXHIBIT D—CONT'D

HOSP. NO.	OBSERVATION WARDS			PROCEDURES BEFORE ADMISSION TO WARDS										
	WARDS	TIME CASES IN OBSERVATION	TIME CASES MAY BE KEPT	THROAT CULTURE B. DIPH.	THROAT CULTURE HEMOLYTIC STREPT.	VAGINAL SMEARS FOR GON.	VON PIRQUET OR MANTOUX	WASSERMANN OR KAHN	SCHICK TEST	DICK TEST	ROUTINE BLOOD COUNTS	URINALYSIS	HISTORY TAKEN	COMPLETE PHYSICAL MADE
Section IV—Continued														
11				Yes	Yes	If indicated	No	Kahn	No	No	Yes	Yes	Yes	Yes
12	None			Yes	No	If indicated			No	No	Yes	Yes	Yes	Yes
13	1 and 2 bedrooms			Yes		Yes		Kahn			Yes	Yes	Yes	Yes
14	None													
15	Yes	3-5 days	As long as necessary			As required			No	No	Yes	Yes	Yes	Yes
16	Yes		Until diag. is established											
17	Yes	Few suspects admitted	Until well at end of quarantine	Yes	Yes	Yes	Occasional	Occasional			Request of staff doctor	3x wk. or daily	Yes	Yes
18	None													

All hospitals in both regions accept both white and negro children. In Region II all are segregated. In Region IV, they are segregated by four hospitals. No hospital in either region limits the number of colored children that may be admitted. Five hospitals have all charity beds. In no hospital are the beds on a strictly paying basis. Five have private rooms for children, 3 have them for adults. Two hospitals have facilities for mothers to stay with the children.

Superintendent.—All of the hospitals derive their funds from either city or county, none from the state. One hospital derives part of its funds from endowment, 2 from private funds, and none receive aid from the community chest. Only 6 hospitals reported their running costs for the last fiscal year. The lowest sum reported was $8,565.31; the highest, $517,631.37. Cost per patient per day varied from $2.22 to $4.68. Average costs for food varied from $0.22 to $1.12 per day. Nursing costs $0.41 to 1.04 per day, and supplies cost from $0.13 to $0.65 per day.

In 12 hospitals the superintendent is a man, a physician in 11, and a lay person in 4. Among 4 women superintendents, 2 are registered nurses, but none are physicians. In one instance, the woman superintendent is also in charge of the nurses' training school.

Nursing.—Among 22 hospitals which replied, 8 are affiliated with other hospitals for the purpose of special training in nursing. Fourteen offer courses in contagious nursing technic. The length of these courses varies from 6 weeks to 3 years. In 6 hospitals only graduate nurses are employed. Immunization of nurses to diphtheria is done in all hospitals of Region II, but is not done in four in Region IV. To immunization of nurses to scarlet fever, in Region II, three replied, "yes" and three, "no"; in Region IV, four, "yes" and twelve, "no." To smallpox immunization in Region II, all replied, "yes"; in Region IV, 13, "yes," and 3, "no." To typhoid fever and other contagious diseases where immunization is possible in Region II, 3 replied, "yes"; in Region IV, 9, "yes." In 1934, one nurse in each of only 2 hospitals in Region II contracted diphtheria, 1 in one hospital, scarlet fever, and none, any other contagious disease. In Region IV, two each in 2 hospitals contracted diphtheria; one, two, three and four, respectively, in 4 hospitals contracted scarlet fever. No other contagious disease was contracted by nurses in any of the 6 hospitals reporting from Region II. In Region IV, 4 hospitals report that nurses contracted rubella, chickenpox, bacillary dysentery, mumps, and one reports that three nurses contracted anterior poliomyelitis. The number of nurses assigned to wards in proportion to the number of patients seems to be adequate in all hospitals. Lengths of assignments vary from 2 weeks to 3 months.

Operating Room.—Fourteen hospitals have at least one special operating room for the contagious division. Only 3 use pupil nurses there. Only 8 hospitals report operations performed in that division in 1934, these varying in number from 7 to 4,070.

Diet Kitchen.—Nine hosiptals have special diet kitchens for infant foods; 6 have them for children.

Supervision Head Nurses

Eight hospitals have head nurses in charge of wards. Fourteen employ one or more graduate nurses for day duty; 11 employ them for night duty.

Supervisors.—Fifteen hospitals employ day supervisors, all of them graduate nurses. Thirteen employ night supervisors, all of them graduate nurses.

Instruction.—Information concerning instruction in contagious nursing was received, but because of the great amount of detailed information we shall not attempt to report it here.

EXHIBIT E

A. GENERAL. II. SUPERINTENDENT

HOSPITAL NUMBER	NUMBER OF BUILDINGS	DATE OF CONSTRUCTION	DATE OF ADDITIONS	NUMBER OF FLOORS IN EACH	FIREPROOF	FIRE STAIRS IN WALLS	OUTSIDE FIRE ESCAPE	COST OF BUILDINGS ONLY
Section II								
1	1	1910 Renovated 1934	None	3	No	No	No	$ 25,000
2	5	1913	None	3 in 3 Bldgs. 1 in 2	Yes	Yes		$1,000,000
3	6	1918 1928 1933		2-4	1		Yes	
4	1	1922		2		Yes		$ 150,000
5	1	1915		2 1 in use	No	No	No	$ 18,000
6								
Section IV								
1	1	1927	None	2	Yes		Yes	
2	Part 2nd floor and a 4-room cottage						Yes	

EXHIBIT E—CONT'D

3	1			4	Yes		Yes	
5	5	New	Not available	3	Partial	Yes	Yes	Not available
6	1	1922	6 beds 1934	1				$ 4,500
7	5 hosp. 12 others	'15-'26 '29-'31 '32-'34	1931 1932	Main—2 Others—1	Main bldg.	No	No	$ 300,000
8		1917 to 1926		3 and basement	Yes			
9								
10	1	1918	0	3	Yes	Yes	Yes	$ 200,000
11	1	1920	1925	1	No			
12					Yes			
13	1	1932						$ 55,000
14	1			2				
15	6	Cont. 1934		5—Main 5—Nurses 1—T.B. 1—Cont.			Yes	$ 400,000
16	1	1912	None	1	No			
17	2	'12-'15		1	No		Yes	$ 30,000
18	1	1910		3	Brick and frame		Porches	$ 85,144

EXHIBIT E

B. BED CAPACITY. II. SUPERINTENDENT

HOSPITAL NUMBER	TOTAL			WARDS	HOW MANY IN CUBICLES	SPECIFY THOSE NOT IN CUBICLES	BEDS IN EACH CUBICLE	CONTAGIOUS CASES EXCLUDED
	BEDS	CRIBS (2 YR. AND UNDER)	BEDS (2 YR. AND OLDER TO 14 YR.)					
Section II								
1	51	15	36	6	All		1	Amebic dysentery, bacillary dysentery, typhoid, Tbc., and syphilis
2	423	22	74	15	1	Isolation—1		None
3	350	24	20	12	Contagious only		1-4	Tbc., syphilis, alcoholism
4	60	10	50	8	None			None
5	14	2	12	3	Movable glass partition used		1	Uncomplicated pertussis, measles, and chickenpox
6								All cases not being handled in homes accepted
Section IV								
1	80	8	6	None				
2	325 25 Communicable	5	10	4	0			None
3	235			7	0			None
5	43	6	37	10	1		1	Whooping cough, measles, chickenpox, unless complicated

EXHIBIT E—CONT'D

6	328	5	As needed	2	8	7 private rooms	1	None
7		10	15	67 rooms	10		1 and 2	None
8	456	26		15	Single rooms to 6 beds			
9	No report							
10	120			4	All		8—3 beds 8—2 beds 1—12 beds 70 single beds	None
11	30	7	23					None
12	18	6	6 adults 6 children	1	All		Varies	None
13	31	6	25			All 1 and 2 beds except 2 rooms in cubicles		None
14	70			4				None
15	228	2		3—Tbc. 2—Cont. 4—Semi-private				None
16	30	2	28	8				Measles, chickenpox, or wh. c. not encouraged
17	60	As needed	As needed	24			16—2 beds 8—3 and 4 beds	None
18	121	5	83 beds 33 cots	8				Accept only diphtheria, smallpox, and scarlet fever

EXHIBIT F

C. DETAILS OF WARD CAPACITY

HOSPITAL NO.	CONTAGIOUS DISEASE WARDS							
	NO. WARDS	TOTAL NO. BEDS	BEDS IN EACH WARD	NO. IN CUBICLES	NO. OF SEPARATE ROOMS	SUNLIGHT	OUTDOOR PORCHES	ADULTS AND CHILDREN IN SAME WARD
Section II								
1	6	51	4-7	All	Only observation rooms	Good except 2 wards	No	No
2	1	79		12	17	Ultra-v. light	Yes	Yes—but not same room
3	4	4-6		24	All cubicles	4 sun parlors	Glass enclosed	No
4	8		4		26	Double doors and large windows	None	According to diagnosis
5	3	10	2-4	Movable partitions		Yes	No	When crowded for space
6					10	Yes	No	Yes
Section IV								
1	2	4	2		None		Yes	Yes
2					Depending on the need	Yes	Yes	No

EXHIBIT F—CONT'D

3	7	235	24 to 39-44	0	59	4	1	Yes
5	10	43	3-7	5	2	East, south and west	Yes	If necessary
6	2	20	5-8	8	7	Outside rooms	No	Yes
7	5	16	3-5	0	When necessary	Yes	1	If necessary
8	2	60	30	None	30	Yes	No	In separate rooms
9	No report							
10	4	120	30			Yes	No	Separate rooms
11	8	30	2-5		1	Yes	No	Occasionally
12	1	18		12		Yes	No	Yes
13	21	31			13 single, 2—3-bed, 6—2-bed	Yes	2	With same disease
14	9	70	6-8		None			Yes
15	3—Tbc. 2—Cont.	17—Cont. 32—Tbc.	3—Cont. 6—Tbc.	0	3 contagious	All	No	No
16	6	28	8 and 4	0	2	Yes	Yes	Yes
17	24	60	2-4	0	24	Indirect	No	Rarely and then if related
18	8		12	0	0	All	9	If necessary

EXHIBIT G

D. ATTENDANCE

HOSP. NO.	PATIENTS		ADMITTED PATIENTS		DISCHARGED		DIED IN HOSPITAL			PATIENTS IN HOSPITAL	
	1932	1933	1934	1932	1933	1934	1932	1933	1934	OPENING LAST YEAR	CLOSE LAST YEAR
Section II											
1	275	Not available	480	Not available	Not available	483	11	Not available	54	21	18
2	11,436	11,852	11,891	11,424	11,873 and died	11,907	966	1,016	1,100	392	373
3	6,268	6,481	7,132	6,236	6,547	7,072				122	144
4	Contagious Tbc.			637 71	920 113	867 75	68 34	83 47	100 26	40	42
5	104	113	July-Jan. 42	104	110	36	0	4	6	1	4
6											
Section IV											
1	1,287	1,260	1,564	1,230	1,394	1,457	52	60	75	45	49
2			84			78			3	0	3
3				4,152	5,095	5,914	415	405	362		

EXHIBIT G—CONT'D

5			561			544			19	36	34
6	3,563	3,673	3,378	3,551	3,678	3,379			326	273	272
7	1,814	2,150	2,191	1,711	2,039	2,050			123	180	166
8	10,405	10,476	10,674				649	699	719	278	278
9											
10	675	742	872	652	675	810	33	53	41	30	51
11	186	211	282	175	201	251	9	9	15	18	23
12		164	166					18	31		
13	192	258	295	190	246	264	19	25	37	12	31
14											
15	101	127	174	116	144	190	30	25	32	29	43
16											
17	275	189		286			1	1			
18	71	56	156	68	57	150	2	0	7	7	13
Totals											
II	18,083	18,446	19,545	18,472	19,563	20,440	1,080	1,150	1,286	576	581
IV	18,569	19,306	20,397	12,131	13,529	15,087	1,210	1,295	1,790	908	963
	36,652	37,752	39,942	30,603	33,092	35,527	2,290	2,445	3,076	1,484	1,544

EXHIBIT G—CONTINUED

D. ATTENDANCE

HOSPITAL NUMBER	COLORED AND WHITE CHILDREN ACCEPTED	COLORED AND WHITE SEGREGATED	LIMIT TO NO. OF COLORED CHILDREN AT ONE TIME	GENERAL PROPORTION COLORED CHILDREN	STRICTLY CHARITY BEDS	STRICTLY PAY BEDS	NO. PRIVATE ROOMS FOR CHILDREN	PRIVATE ROOMS FOR ADULTS	ANY FACILITIES FOR MOTHERS TO STAY WITH CHILDREN
Section II									
1	Yes	Yes	Only as to space and beds	¼%	51	None	Rare exceptions	Rare exceptions	No
2	Yes	Yes	No	40%	All	None	Emergency Private cases rarely adm.	Emergency Private cases rarely adm.	No
3	Yes	Yes	No		341 and pay				
4	Yes	Yes	No	⅖%	All and private accepted				No
5	Yes	Yes	No	¾%	14	None			No
6	Yes	Yes	No	60%			2	2	No
Section IV									
1	Yes	Yes	No	100:1	Varies	Varies	19	19 for both	Yes
2	Yes	No	No		All	None	2	2	No
3	Yes	No	No						No
5	Yes	No	No	Less than 1%	43 Cont.	None	None	None	No
6	Yes		No	Low	All except for private	As needed			No

EXHIBIT G—CONT'D

7	Yes	As far as possible	No	Very few	225	10 beds part pay	None	1	No
8	Yes	No	No	Not known	All	None	None	None	No
9	Yes	No	No	About 1%					Yes
10	Yes	No	No	2 or 3 a yr.	120	None			No
11	Yes	No	No	Practically more have colored	All	None	None	None	No
12	Yes	No	No	negligible		None			No
13	Yes	As far as possible	No	Small	31				No
14	Yes	No	No	1:10	If unable to pay	All unless unable to pay	None	None	No
15	Yes	No	No	Small	17	None	Not segregated	Not segregated	No
16	Yes	No	No	1:300	30	None	Not segregated	Not segregated	Yes, but not permitted
17	Yes	Not always	No need	1:20	All	None	None	None	If both with same disease
18	Yes		No need		Residents no charge	None	None	None	If absolutely necessary

EXHIBIT H

IV. X-RAY

HOSPITAL NUMBER	DIAGNOSTIC FACILITIES	FULL-TIME TECHNICIANS	AVAILABLE ANY HOUR	AT WHAT HOURS	HIGH-SPEED RADIOGRAPHY	MILLI-AMPERAGE	SUPERFICIAL RADIOGRAPHY	VOLTAGE	DEEP RADIOTHERAPY	VOLTAGE	FLUOROSCOPY	STEREOSCOPIC PLATES
Section II												
1	Yes	2	Yes		Yes	100	Therapy	50-90 Kw	Yes	To 200,000 Kv	Yes 2	Yes
2	Yes	3	Yes		Yes	Ma nax 3,500	Yes	Kv Pk 30 & up	Yes	30-90 Kv	Yes	Yes
3	Yes	1	Yes		Yes		Yes		No		Yes	Yes
4	Yes	1	Yes	All	Moderately high	100	Therapy	All	Yes	185 Peek Kv	Yes	Yes
5	Yes	1	Yes	All	Yes	500	Yes	140 Kv	Yes	200 Kv	Yes	Yes
6	None											

EXHIBIT H—CONT'D

Section IV

1	Yes	No	Yes		Yes	200	No		No		Yes	Yes
2	Yes	1	Yes		Yes		Yes	125 Kv	No		Yes	Yes
3	Yes	1	Yes								Yes	
5	Yes	2	Yes		No		Therapy	100-125	Yes	200 Kvp	Yes	Yes
6	Yes	1	Days	8-5	Yes	100	Yes	30 Kvp up	Yes	200 Kvp	Yes	Yes
7	Yes	1½	Yes		Yes	100 ma	Yes	35 Kvp	No		Yes	Yes
8	Yes	2		7:30 A.M. 4:30 P.M.	No	100	Yes	130 Kvp	Yes	200 Kvp	Yes	Yes
9			Yes						Yes		Yes	Yes
10	Yes	4	Yes	7:30 A.M. 12:00 M.	Yes	200	Yes	20 Ko to 100 Ko	Yes	200 Ko	Yes 2	Yes
11	Yes	3	Yes		Yes	100	Yes		No		Yes	
12	Yes	2	Yes		Yes		No		No		Yes	Yes
13	Yes	1 part time	Yes		Yes		No		No		Yes	Yes
14	None											
15	Yes	2	Yes		Yes	100	Yes	92-102 Kvp	No		Yes	Yes
16	None											
17	Yes	1	No	8-4	Yes	100	Yes		No		Yes	Yes
18	None											

IV. X-Ray

HOSPITAL NUMBER	PORTABLE X-RAY MACHINE	INTERNES X-RAY WORK	IF SPECIAL SPECIFY	EQUIPMENT ADEQUATE	DEPT. SERVE DISPENSARY	OUTSIDE PHYSICIANS	NO. X-RAY PLATES LAST YEAR	NO. SUPERFICIAL TREATMENTS	NO. DEEP THERAPY TREATMENTS
Section II									
1	Yes 2	No		Yes	Yes	No	Unable to ascertain	Included with Grady Hosp.	With Grady Hosp.
2	Yes	No		Yes	Yes	No	50,000	100	200
3	Yes	Some	Special	Yes	Yes	Indigent cases			
4	No	Yes	Attend reading all films and fluoroscopic exams if interested	Old and space not had at present	Yes		Plates not known 8,176 exams.	Total 2,878	
5	Yes	No		Yes	Yes	Yes	4,636	396	793
6	None								
Section IV									
1	No	No		Yes	Yes	Yes	597	0	0
2	No	No		Yes except deep therapy	Yes	No	Communicable diseases not segregated		
3	Yes	No		Yes	No		1,400		

EXHIBIT H—CONTINUED

5	Yes	No		Yes	Yes	No	Communicable diseases not segregated		
6	Yes	No		Yes	Yes	Charity only	2,904 Exam. of film	131	170
7	No	No		For special work insufficient	No	No	3,068 729 dentals	341	0
8	No	No		Yes	No	No	18,440	371	1,580
9	Yes		7 weeks' instruction diagnoses of films	Yes	Yes	Yes			
10	2	No		Business too great for equipment	Yes	City physicians only	N.R.	0	0
11	Yes	Yes	Emergency	Yes	Yes	No		682	0
12	Yes	No		Yes	Yes	No			
13	Yes	No		Yes	Yes	No		0	0
14									
15		Fluoroscopic examinations on fractures		Deep therapy apparatus necessary	Yes	No	Contagious comparatively few	0	0
16									
17	No	No		Yes	No	Through City Health		0	0
18									

Information concerning crossed infections in 1934.

Diphtheria:	14 hospitals—occurred in one
Scarlet fever:	14 hospitals—occurred in five
Measles:	14 hospitals—occurred in one
Pertussis:	13 hospitals—occurred in one
Chickenpox:	13 hospitals—occurred in one
Other diseases:	11 hospitals—occurred in none

X-ray (Exhibit H).

Four hospitals have no x-ray diagnostic facilities. Sixteen have these facilities available at any hour, day or night. Fifteen are equipped for high-speed radiography, 14 for superficial, and 9 for deep radiotherapy. Nineteen are equipped with fluoroscopes, 17 for stereoscopy and 12 have portable machines. Internes do x-ray work in 3 hospitals. Seventeen consider their equipment to be adequate. The x-ray department serves the dispensary in 15 hospitals and outside physicians in 3.

Again our information indicates that these departments in many instances serve an entire general hospital; hence, figures given for number of treatments, plates, etc., are not satisfactory for comparison or estimation of these actually in the contagious department alone.

Laboratories—Pathological—Clinical—Bacteriological—Serological

General.—Thirteen hospitals indicate that a full-time director in charge of laboratories is employed. In 3 the work is done in the city health department, while 7 employ part-time directors.

Pathological.—Twelve hospitals have full-time directors of pathological laboratories. Three have no directors either full or part time. Sixteen employ full-time technicians, 3 have none on full time. Internes do laboratory work in 9 hospitals, routine in 3, special in 6, routine and special in 1. Seventeen of the 19 hospitals that replied consider their laboratory facilities adequate. Only 9 have facilities for research work. Autopsy percentages among 15 hospitals reporting varied from about 30 to a little less than 60 per cent, with a general rough average around 50 per cent.

Clinical.—Fifteen hospitals have full-time directors of the clinical laboratories, 6 have part-time directors, and the others have none or did not reply. Twenty hospitals have full-time technicians, and in 14, the internes do work in the clinical laboratory, routine in 8, and special in 6. Blood chemistry work is available in 20 hospitals; 7 have "fume hoods"; and 16 have colorimeters. Nineteen possess equipment to do basal metabolic tests. The machines used are usually Sanborn or McKesson's. Seventeen consider their clinical laboratory facilities to be adequate, 2 do not, and 2 do not reply. Twelve afford facilities for research work.

Bacteriological.—Fifteen hospitals have full-time directors of the bacteriological laboratories; four have part-time directors. Nineteen have full-time technicians. Internes do laboratory work in 10, in 5, routine, in 5, special. Nineteen laboratories have electric incubators. Eighteen make all or part of their own media. Nineteen keep animals for experimental purposes. Eighteen have facilities for research work. Eleven consider their bacteriological laboratory facilities adequate.

Serological.—Fifteen hospitals have full-time directors of the serological laboratories and 18 have full-time technicians. Internes do laboratory work in only 2, and this is of a special nature in both instances. Wassermanns are done in their own laboratories in 17, and Kahn tests in 14. Seventeen consider their facilities adequate, and 9 have facilities for research work.

Miscellaneous.—Fourteen hospitals have facilities available for simple photography, 4 for color photography, and 4 for motion pictures. An electrocardiograph is available in 17 hospitals.

Diet Kitchen.—Fourteen hospitals employ trained dietitians. Five employ nurses in this capacity; the remainder did not reply. In 6 hospitals, diets are arranged by both attending physicians and dietitians; in 7, the attending physician alone prescribes the type of diet. One gains the impression that diets are efficiently supervised in most of these hospitals.

Social Service.—Fourteen hospitals maintain a social service department. All but one have a full-time worker in charge, and in most instances these supervisors have had special training for that work.

Fourteen hospitals investigate all patients who are admitted. This is usually done by talking to relatives who bring the patients, but by 9 hospitals home visits are made. Thirteen hospitals take a complete social history in all cases, which is, by 7, filed with the medical history. In 4 an abstract is filed. The social service investigates the patient's ability to pay in 14 hospitals. Convalescent homes are available for patients from 5 of the hospitals, foster homes for 11 hospitals. Only 2 consider their facilities for convalescent care to be adequate.

By 11 hospitals, cases are "followed" after discharge. The social service assists in getting patients for recall or "follow-up" in 12 hospitals. Volunteers are used for indoor work by 7, for outdoor work by 3. The ward service department is supported by hospital funds in 15, by outside funds in 1; the rest do not reply. Only 2 hospitals have a special "lay" committee in charge of the social service department, a physician being on this committee in 1 instance.

General Information (1934).—The following chart reveals the number of cases of the more usual contagious diseases admitted to these hospitals during 1934, together with the total deaths and the percentage death rate in all hospitals for each disease (Exhibit I).

Only 800 cases of diphtheria were admitted to all hospitals in both regions, and of these only 266 were admitted in Region IV. The percentage of deaths was about the same for the 2 regions, but slightly higher for Region II than for Region IV. Scarlet fever deaths show about the same percentage in each region. Measles shows an extremely low rate for Region IV, and both regions had lower percentages of deaths than did Region III. Pertussis has a very high rate in Region II. Both regions are higher than Region III, provided one hospital is omitted which had the remarkable record of only 0.4 per cent deaths among 1,824 cases. There were no deaths from smallpox in either region. This was also true in Region III. There were no deaths from chickenpox in Region IV and only 0.1 per cent in Region II, but here again 1 hospital, the same hospital mentioned in connection with pertussis, reports no deaths among 1,183 cases. Eliminating these figures, the death rate in the rest of the hospitals in Region IV is 3.3 per cent. Percentage of deaths for epidemic spinal meningitis is considerably higher in both regions than in Region III. Typhoid fever percentages are higher in Region II and lower in Region IV than those reported for Region III.

Amebic dysentery occurred with relative infrequency in these two regions considering the area of country involved. The percentage of deaths was about the same, 7.1 per cent and 6.2 per cent respectively. Region III reported more than twice as many cases with no deaths (mortality questionable).

Bacillary dysentery occurred much more frequently in Region II and the percentage of deaths was almost three times as great.

Among other diseases listed under miscellaneous, only 2 cases of poliomyelitis were reported from Region II with no deaths, but Region IV reported 251 cases with 18 deaths, a percentage of 7.1 per cent. Region IV reports 174 cases of erysipelas with a death rate of 10.5 per cent.

As in Region III, other contagious diseases more frequently admitted to the contagious hospitals of Region II and IV are encephalitis, mumps, influenza, strepto-

EXHIBIT I

VIII. GENERAL INFORMATION—1934

HOSPITAL NUMBER	DIPHTHERIA		SCARLET FEVER		MEASLES		WHOOPING COUGH		SMALLPOX		CHICKEN-POX		EPI. CEREBRO-SPINAL MENINGITIS		TYPHOID FEVER	
	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS
Section II																
1	273	17	73	1 (pneumonia)	104	7	30	5	0	0	8	0	27	12		
2	127	19	96	2	53	2	40	6	0	0	16	0	5	1	30	4
3	28	1	15	0	11	0	3	0	0	0	8	0	2	2	14	1
4	55	5	50	0	161	7	48	12	4	0	14	0	20	11	69	17
5	35	1	21	0	0	0	32	6	0	0	2	0	3	2	8	0
6	16	4	23	0	23	0	6	0								
Per cent of fatal cases	8.8%		1.08%		4.5%		18.2%		0.0%		0.0%		49.1%		18.1%	
Section IV																
1	4		3													
2	13	3	13	0	2	0	0	0	0	0	4	0	0	0	11	0
3	No report															

EXHIBIT I—CONT'D

5	67	2	112	2	53	1	4	0	0	0	1	0			51	2
6	30	5	36	1	10	0	0	0	7	0	0	0	0	0	0	0
7	3	0	19	0	15	0	7	0	0	0	2	0	1	1	25	0
8	46	3	69	0	16	0	3	0	0	0	3	0	11	4	9	1
9	No report															
10	33	0	106	6	54	0	35	2	0	0	12	1	5	3	7	0
11	20	0	40	2	24	0	24	2	4	0	6	0	3	3	3	0
12	31	2	40	2	10	0	8	1	0	0	10	0	0	0	25	8
13	11	3	75	1	39	0	27	3	0	0	18	1	3	3	28	8
14*	9	-	578	-	2	-	-	-	32	-	-	-	1	-	-	-
15	0	0	61	3	20	3	18	5	4	0	2	0	2	1	8	2
16	8	0	32	1	2	0	3	0	11		2		1	0	2	0
17	1	0	611	3	275	1	1824	8	135	0	1183	0	2	1	30	0
18	0	0	83	2					4	0						
Per cent of fatal cases																
	7.0%		1.8%		0.96%		1.07% 10.07% without No. 17				0.1% or 3.3% without No. 17		55.1%		10.5%	

*Does not report deaths. Hence mortality rate is figured without them.

EXHIBIT I—CONT'D

VIII. GENERAL INFORMATION—1934

MISCELLANEOUS DISEASES

HOSPITAL NUMBER	DISEASES	CASES	DEATHS
Section II			
1	Encephalitis	2	0
	Vincent's angina	3	0
	Tetanus	3	2
	Anterior poliomyelitis	2	0
	Mumps	4	0
2			
3	Acute colitis	5	1
	Diarrhea	5	0
4			
5			
6			
Section IV			
1	Influenza	2	
	Poliomyelitis	1	
	Streptococcic throat	2	1
2	Malta fever	5	0
	Influenza	5	0
	Diphtheria carrier	1	0
3			
5	Poliomyelitis	35	0
	Erysipelas	18	2
	Trachoma	19	
	Gc. vaginitis juveniles	5	
	Other Gc. infections	46	
	Other diseases	180	7
6	Erysipelas	10	1
	Lobar pneumonia	23	8
	Poliomyelitis	8	0
	Meningitis	5	5
	Other diseases	8	1
7	Balantidium dysentery	1	0
	Poliomyelitis	2	1
	Trachoma	1	0
	Mumps	1	0
	Leprosy	2	0
8	Erysipelas	27	2
	Encephalitis	5	1
	B. welchii	11	1
	Gc. ophthalmia	5	0
	Other diseases	133	13
9			

EXHIBIT I—CONT'D

10	Erysipelas	55	3
	German measles	11	0
	Gc. vaginitis	32	0
	Gc. ophthalmia	7	0
	Other diseases	269	21
		163	0
11	Gc. vaginitis	10	0
	Impetigo	8	0
	Scabies	16	0
	Vincent's angina	5	0
	Poliomyelitis	17	0
	Other diseases	17	2
12	Anterior poliomyelitis	4	1
13	Poliomyelitis (fiscal year)	17	2
	July-December	9	3
	Impetigo contagiosa	15	1
	Erysipelas	14	3
	Tbc. meningitis	6	4
	Other diseases	4	4
14	Impetigo	1	
	Mumps	3	
	Poliomyelitis	3	
	Erysipelas	41	
15	Influenza	3	0
	Syphilis	64	0
	Tetanus	54	17
	Rheumatic fever	7	0
	Other diseases	179	9
16	Poliomyelitis	6	2
	Tbc. meningitis	1	1
	Other diseases	16	0
17	Erysipelas	9	2
	Poliomyelitis	91	7
	Mumps	2916	0
	German measles	8	0
18	Poliomyelitis	69	5
	Poliomyelitis	253	18
		7.1%	
	Erysipelas	174	133-14
		10.5%	

EXHIBIT I—CONT'D

VIII. GENERAL INFORMATION—1934

HOSPITAL NUMBER	AMEBIC DYSENTERY		BACILLARY DYSENTERY	
	CASES	DEATHS	CASES	DEATHS
Section II				
1				
2	4	0	18	1
3				
4	6	1	65	19
5	4	0	4	1
6				
Per cent of fatal cases	7.1%		24.1%	
Section IV				
1			1	
2	8	0	8	0
3	No report			
5	3	1	3	1
6	3	0	0	0
7	3	0	0	0
8	5	0	0	0
9	No report			
10				
11	0	0	4	0
12	3	0	2	0
13	7	1	1	0
14				
15			1	0
16				
17	N.R.	3	N.R.	1
18				
Per cent of fatal cases	6.2%		8.3%	

coccic throat infections, Vincent's angina, various forms of meningitis and gonorrheal vaginitis in juveniles. None report that syphilitic cases are admitted, but only 2 say that they are barred.

COMMENT

Regions II and IV include the southern states and the Far West. In this entire area, we found only 27 contagious hospitals listed as such. The report is based on replies received from 23 hospitals, representing 9 states, 5 in Region II and 4 in Region IV. No city in either of the 2 regions has more than 1 contagious-disease institution with the exception of San Francisco, California, which lists 2. Among 17 hospitals, of the total number reported from Region IV, 12 are found in California. The figures indicate that there are states in both Regions II and IV which have no contagious-disease hospitals.

There are only three large hospitals in the 2 regions, each of these having more than 300 beds, none more than 475.

Eighteen of the hospitals employ resident physicians and 6 have an active service and employ more than 1 resident physician. Several hospitals unfortunately do not require the resident physician to have had previous hospital experience. The larger hospitals all require at least one year of previous hospital experience before the

applicant can be eligible for that position. All hospitals require their internes to have M.D. degrees. Services of one year's duration or more are available in only 8 hospitals.

The contagious hospital is connected with a medical school or affords training to medical students or both in the following cities: Atlanta, Ga., Louisville, Ky., Memphis, Tenn., Galveston, Tex., Los Angeles, Calif., San Francisco, Calif. (2), Portland, Ore., and Salt Lake City, Utah. Facilities for research work are available to the resident and home staff in only the larger hospitals and among these hospitals, as a rule, the organization, particularly as to clinical laboratory and x-ray facilities, appears to be efficient.

Several hospitals apparently do not take routine throat cultures, vaginal smears, or blood counts. We feel that these 3 procedures, at least, should be routine in all contagious hospitals.

Only 8 hospitals have nursing affiliations that afford training in contagious nursing. As in Region III, comparatively few nurses contracted a contagious disease while working in these hospitals.

Several hospitals do not report that they have operating rooms in the contagious divisions, which we feel are very essential parts of contagious hospitals.

Fourteen hospitals reported concerning crossed infections. The record shows that these were comparatively infrequent.

Four hospitals among 23 apparently have no facilities for x-ray work. This is a serious weakness, although these are small tax-supported institutions as in Region III in which the need for x-ray work is probably infrequent. Among the smaller hospitals, again the laboratory services often seem inadequate.

We realize that among small institutions the cost of maintaining a highly organized laboratory, nursing and dietary service would probably be prohibitive, when the relatively small number of cases admitted yearly is considered. However, the patient who is ill of a contagious disease deserves and should have just as efficient care as any other sick person. If an institution for the care of contagious diseases is to be maintained at all, it should be established and run upon that principle. Finally, all of the institutions but two report that their facilities for convalescent care are not adequate.

In general, we might say that most of these institutions seem well equipped and are well run.

Book Review

Allergy of the Nose and Paranasal Sinuses. By FRENCH K. HANSEL, St. Louis, 1936, The C. V. Mosby Company, 820 pages with 58 text illustrations and 3 color plates.

As stated in the Preface, "the object of this monograph is to familiarize the otolaryngologist with the clinical features of allergy as related to the field of otolaryngology, to review the various phases of the subject itself, and to point out the frequent association of the nasal with the other manifestations, particularly asthma, gastrointestinal allergy, allergic skin diseases, and allergic headache." A chapter of twenty-five pages is devoted to allergy and infection of paranasal sinuses in children. This chapter should make the book of considerable interest to all pediatricians.

The subject matter is divided into four general sections. Under the major heading of Fundamental Principles of Paranasal Sinus Diseases, the author discusses the physiology, biochemistry, and bacteriology of the nose and paranasal sinuses. The pharmacologic action of drugs and the cellular reactions of the tissues in allergy and in immunity are described. The second section is devoted to a brief but comprehensive discussion of the theoretical phases of allergy and anaphylaxis and the fundamental clinical characteristics of allergy. In this section, the author presents the conservative, generally accepted ideas which prevail today on this very complex and little understood subject. The third section is devoted to clinical manifestations of allergy as they are expressed in the nasal and paranasal sinus areas of the body. This section of the book probably represents the best efforts of the author, and one will find here excellent discussions of diagnosis of these various conditions. Hay fever is dealt with as a separate section, but may be included for consideration in this section on clinical manifestations. At least as far as children are concerned, it seems difficult to separate nasal pollen reactions from those caused by other foreign substances. The fourth section is devoted to treatment of these various clinical conditions.

The form of the book is entirely satisfactory. The type is large, clear, the style is simple and direct, though inclusive, and the text is easy to read. There are numerous good illustrations which are usually original. There is ample reference to the best work of the most conservative workers, and it would seem that very little of importance in the literature has been missed. Each chapter has an extensive bibliography on that subject. The author has also included to great advantage a résumé, representing his opinion of each phase of the subject. This feature makes the book extremely useful for rapid reference. Numerous case reports in detail are included to illustrate more complex points. These are from the author's own experience in a large otolaryngologic clinic. Part of the pediatric material has been drawn from cooperation with the pediatric allergist.

The work represents a very valuable contribution to this field of medicine. It is recognized that only the beginning of allergy is at present understood and that many factors are mixed with theory and hypothesis, all of which are influenced by personal opinion and experience. These ideas are changing rapidly, and, no doubt, many statements in the book will be questioned in some degree. The general principles, however, are all recognized. It would be difficult to find one person who could combine in his experience all the phases of this very broad subject.

The book should be of value to the otolaryngologist, but it would seem to this reviewer that it would be still more useful to anyone in clinical medical practice, either the internist, the pediatrician, or the general family doctor. The book has considerable reference value and the information is sufficient to be instructive to anyone.

H. McC.

The Journal of Pediatrics

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